09/543441

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Snyder
U.S. Patent No.	6,342,482
Issue Date:	January 29, 2002
Title:	Formulations For Controlling Human Lice
Assignee:	Eli Lilly and Company
Attorney Docket No.	X12227A_US

Certificate Under 37 CFR 1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as express mail, Express Mail No. EV 404 968 626 US in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on March 17, 2011

(Signature)

Eric E. Williams
(Printed Name)

TRANSMITTAL FOR APPLICATION FOR EXTENSION OF PATENT

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing is an Application for Extension of Patent Term Under 35 U.S.C. § 156 with respect to the above-captioned patent.

Applicant, the assignee of the above-referenced patent, on this day has simultaneously filed two related applications for extension of patent term under 35 U.S.C. § 156, including the present application referenced in the caption above. These two patent term extension applications relate to U.S. Patent Nos. 6,063,771 and 6,342,482 for New Drug Application No. NDA 022408.

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Applicant respectfully requests if the Commissioner determines both of U.S. Patent Nos. 6,063,771 and 6,342,482 are entitled to a patent term extension under the same regulatory review period, the Commissioner establish a time period in accord with the policies set forth in MPEP § 2761 within which the Applicant will be permitted to elect the patent for which extension is desired and/or to voluntarily withdraw an application. At that time, Applicant

will elect and withdraw applications for patent term extension, as appropriate, to ensure only one patent is extended for NDA 02240, and such that a given patent obtains only one extension under 35 U.S.C. § 156.

Pursuant to 37 C.F.R. § 1.740(b) and MPEP § 2753, a total of three copies of the application for patent term extension are submitted herewith.

The Commissioner is hereby authorized to charge the filing fee of $1,120.00 and any additional fees which may be required by this or any other related paper, or credit any overpayment to Deposit Account No. 05-0840 in the name of Eli Lilly and Company and any additional fees which may be required.

Respectfully submitted,

/James J. Sales/
James J. Sales
Attorney Reg. No. 33,773

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Snyder
U.S. Patent No.	6,342,482
Issue Date:	January 29, 2002
Title:	Formulations For Controlling Human Lice
Assignee:	Eli Lilly and Company
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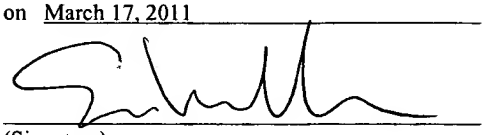
on March 17, 2011



(Signature)

Eric E. Williams
(Printed Name)

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156, Eli Lilly and Company (hereinafter "Lilly"), owner of the above-identified patent, hereby requests an extension of the patent term of U.S. Patent No. 6,342,482. Applicant Lilly is the owner of U.S. Patent No. 6,342,482 according to the following chain of title.

1. The above-captioned patent arises from an application filed as a "continuation" of U.S. Patent Application No. 09/338,116 (hereinafter, the "parent patent application"), now U.S. Patent No. 6,063,771. Assignment of all rights of inventor Daniel Earl Snyder to Eli Lilly and Company in the parent patent application and in "continuations" thereof is evidenced by virtue of an Assignment recorded in the U.S. Patent and Trademark Office on June 22, 1999, at Reel 010056, Frame 0605. That Assignment is effective to transfer the inventor's rights in the above-captioned patent to Eli Lilly and Company.

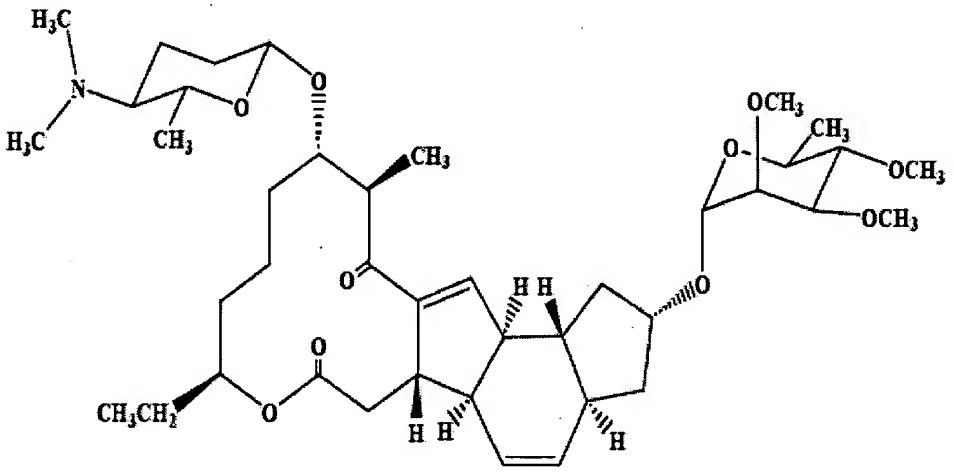
The U.S. Patent and Trademark Office Patent Assignment Abstract of Title for U.S. Patent No. 6,063,771 (*i.e.*, the patent issued from the parent patent application) is attached hereto as Exhibit A.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 *et seq.* and follows the numerical format set forth in 37 C.F.R. § 1.740(a):

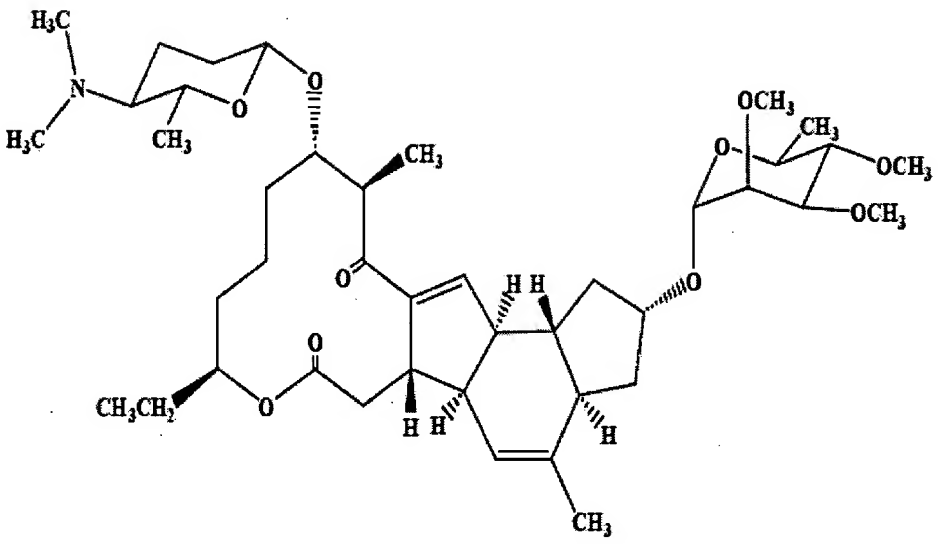
(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is spinosad. Spinosad is a mixture of spinosyn A and spinosyn D in a ratio of approximately 5 to 1 (spinosyn A to spinosyn D).

Spinosyn A has the chemical name 1H-as-indaceno[3,2-d]oxacyclododecin-7,a5-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino) tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-, (2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-. Spinosyn A has the following structure:



Spinosyn D has the chemical name 1H-as-indaceno[3,2-d]oxacyclododecin-7,15-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino) tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-, (2S,3aSR,5aS,5bS,9S,13S,14R,16aS,16bS)-. Spinosyn D has the following structure:



Spinosad is the active ingredient in the product NATROBA™ as may be seen from attached Exhibit B, which is a copy of the labeling information for the approved product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under Section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. § 301 *et seq.* Section 505 provides for the submission and approval of new drug applications (NDAs) for drug products meeting the definition of "new drug" under Section 201(p) of the Act.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Spinosad was approved by the Food and Drug Administration (FDA) for commercial marketing pursuant to Section 505 of the FFDCA on January 18, 2011.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement

of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved:

As stated in Sections 1, 2, and 3 above, the active ingredient in the product NATROBA™ is spinosad. Spinosad was not previously approved for commercial marketing or use under Section 505 of the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act. Spinosad was approved for commercial marketing or use for the topical treatment of head lice infestation under Section 505 of the FFDCA on January 18, 2011.

For full disclosure, spinosad was previously approved for commercial marketing or use under Section 512 of the FFDCA according to New Animal Drug Applications (NADAs) No. 141-277 and No. 141-321.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted:

The product was approved on January 18, 2011 and the last day within the sixty-day period permitted for submission of an application for extension of a patent is March 18, 2011. Accordingly, this application is timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

Inventor:	Daniel Earl Snyder
U.S. Patent No.:	6,342,482
Issue Date:	January 29, 2002
Expiration Date:	June 22, 2019

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings:

A copy of the patent is attached as Exhibit C.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

A copy of a terminal disclaimer filed in the U.S. Patent Office on August 24, 2001, for the above-captioned patent is attached as Exhibit D. No maintenance fees are outstanding for this patent. A statement evidencing the two maintenance fee payments for the patent is enclosed as Exhibit E.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: (i) The approved product, if the listed claims include any claim to the approved product; (ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and (iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product:

U.S. Patent No. 6,342,482 claims a formulation of the approved product, which is spinosad.

The applicable claims are at least claims 1-6.

In general terms, claims 1-6 recite a pediculicidal (*i.e.*, destructive to lice) hair conditioner formulation. The manner in which claims 1-6 reads on the approved product is as follows:

Claim 1:

Claim 1 recites the following:

> A pediculicidal hair conditioner formulation comprising as an active ingredient from about 0.1% to about 30% of a spinosyn, or a physiologically acceptable derivative or salt thereof, a conditioner and water.

Claim 1 reads on the approved product because the approved product is a pediculicidal conditioner formulation. The approved product comprises an active ingredient of spinosad (*i.e.*, a mixture of spinosyn A and spinosyn D) that is present at 0.9%, a conditioner (stearyl dimethyl benzyl ammonium chloride combined with cetearyl alcohol), and water.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product: (A) The effective date of the investigational new drug (IND) application and the IND number; (B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and (C) The date on which the NDA was approved or the Product License issued;

(ii) For a patent claiming a new animal drug: (A) The date a major health or environmental effects test on the drug was initiated, and any available substantiation of that date, or the date of an exemption under subsection (j) of Section 512 of the Federal Food, Drug, and Cosmetic Act became effective for such animal drug; (B) The date on which a new animal drug application (NADA) was initially submitted and the NADA number; and (C) The date on which the NADA was approved;

(iii) For a patent claiming a veterinary biological product: (A) The date the authority to prepare an experimental biological product under the Virus-Serum-Toxin Act became effective; (B) The date an application for a license was submitted under the Virus-Serum-Toxin Act; and (C) The date the license issued;

(iv) For a patent claiming a food or color additive: (A) The date a major health or environmental effects test on the additive was initiated and any available substantiation of that date; (B) The date on which a petition for product approval under the Federal Food, Drug, and Cosmetic Act was initially submitted and the petition number; and (C) The date on which the FDA published a *Federal Register* notice listing the additive for use;

(v) For a patent claiming a medical device: (A) The effective date of the investigational device exemption (IDE) and the IDE number, if applicable, or the date on which the applicant began the first clinical investigation involving the device, if no IDE was submitted, and any available substantiation of that date; (B) The date on which the application for product approval or notice of completion of a product development protocol under Section 515 of the Federal Food, Drug, and Cosmetic Act was initially submitted and the number of the application; and (C) The date on which the application was approved or the protocol declared to be completed:

According to the provisions of 37 C.F.R. § 1.740(10)(i), the relevant dates and information to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(A) On October 8, 2004, ParaPRO, a licensee to the above-captioned patent, submitted Investigational New Drug (IND) No. 66,657 (Spinosad Crème Rise for the Treatment of Human Head Lice) to the FDA to permit interstate shipment of spinosad for the purpose of conducting clinical studies to support the approval of a subsequent NDA for spinosad. A copy of the letter transmitting the IND to the FDA is attached as Exhibit F. The FDA acknowledged receipt of and accepted the IND on October 12, 2004. According to Subsection (i)(2) of Section 505 of the FFDCA, clinical investigation of a new drug may begin thirty days after the FDA's receipt of the IND application from the sponsor, provided that the FDA does not determine a clinical hold is necessary. A clinical hold was not issued for IND No. 66,657. Accordingly, the IND became effective thirty days after the date of the FDA's receipt on October 12, 2004. This establishes the beginning of the "regulatory review period" under 35 U.S.C. § 156(g)(1) as November 11, 2004, the effective date of an exemption under Section 505(i).

(B) On January 21, 2009, ParaPRO LLC submitted an NDA for spinosad, NDA No. 022408. A copy of the letter transmitting the NDA is attached as Exhibit G. The NDA submission was received by the FDA on January 22, 2009 as indicated by Exhibit H. Thus, for the purposes of the "regulatory review period" under 35 U.S.C. § 156(g)(1), January 22, 2009 is the date of initial submission of a new drug application under Section 505 for spinosad.

(C) NDA No. 022408 was approved on January 18, 2011. Attached as Exhibit I is a letter dated January 18, 2011 from the FDA to ParaPRO LLC approving the NDA for spinosad. Thus, for the purposes of the "regulatory review period" under 35 U.S.C. § 156(g)(1), January 18, 2011 is the date of approval of the new drug application for spinosad submitted on January 22, 2009.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

During the applicable regulatory review period, ParaPRO LLC, a licensee to the above-captioned patent, was actively involved in obtaining NDA approval for spinosad. As discussed in paragraph (10) above, the IND for spinosad was submitted on October 12, 2004, the NDA was submitted on January 21, 2009, and the NDA was approved on January 18, 2011. ParaPRO LLC was in close consultation with the FDA during the clinical studies conducted under the IND. Similarly, subsequent to the submission of the NDA, ParaPRO LLC had numerous contacts and meetings with the FDA with respect to the approval and, in fact, conducted additional studies at FDA's request to support the NDA approval. The description of significant activities undertaken by ParaPRO LLC with respect to spinosad during the regulatory review period is set forth in Exhibit J and is illustrative of the activities involved.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined:

(a) Statement of eligibility of the patent for extension under 35 U.S.C. § 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. § 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) The term of U.S. Patent No. 6,063,771 expires on June 22, 2019. This application has, therefore, been submitted before the expiration of the patent term.

(2) The term of this patent has never been extended.

(3) This application is submitted by the owner of record, Lilly (according to the assignment recorded in the U.S. Patent and Trademark Office on June 22, 1999, at Reel 010056, Frame 0605). This application is submitted in accordance with 35 U.S.C. § 156(d) in that it is submitted within the sixty-day period beginning on the date, January 18, 2011, the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. § 156(d).

(4) As evidenced by the January 18, 2011 letter from the FDA (Exhibit I), the product was subjected to a regulatory review period under Section 505 of the FFDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of spinosad after regulatory review under Section 505 is the first permitted commercial marketing of spinosad. This is confirmed by the absence of any new drug application approved under Section 505 for spinosad prior to January 18, 2011. For full disclosure, spinosad was previously approved for commercial marketing or use under Section 512 of the FFDCA according to New Animal Drug Applications (NADAs) No. 141-277 and No. 141-321.

(b) Statement as to length of extension claimed:

The term of U.S. Patent No. 6,063,771 should be extended by 1493 days to July 24, 2023. This extension was determined on the following basis: as set forth in 35 U.S.C. § 156(g)(1) and 37 C.F.R. § 1.775(c), the regulatory review period equals the length of time between the effective date of the initial IND on November 11, 2004 and the initial submission of the NDA on January 22, 2009, a period of 1533 days, plus the length of time between the initial submission of the NDA on January 22, 2009 to NDA approval on January 18, 2011, a period of 726 days. These two periods added together equal 2259 days.

Pursuant to 35 U.S.C. § 156(c) and 37 C.F.R. § 1.775 (d)(1)(i), the term of the patent eligible for extension shall be extended by the time equal to the regulatory review period which occurs after the date the patent was issued. The entire period under 35 U.S.C. § 156(g)(1)(B) occurred after the May 16, 2000 issue date of U.S. Patent No. 6,063,771. Thus, the 2259-day period calculated above as the term of the patent eligible for extension should not be reduced under 35 U.S.C. § 156(c) or 37 C.F.R. § 1.775(d)(1)(i).

As discussed in paragraph (11) above and as illustrated in Exhibit J, ParaPRO, a licensee to the above-captioned patent, was continuously and diligently working toward securing NDA approval for spinosad. As ParaPRO acted with due diligence during the entire period of regulatory review, the 2259-day period calculated above as the term of the patent eligible for extension should not be reduced for lack of diligence under 35 U.S.C. § 156(c)(1) or 37 C.F.R. § 1.775(d)(1)(ii).

Pursuant to 35 U.S.C. § 156(c)(2) and 37 C.F.R. § 1.775(d)(1)(iii), this 2259-day period is to be reduced by one-half of the time from the effective date of the initial IND (November 11, 2004), or the date of issue of U.S. Patent No. 6,063,771 (May 16, 2000), whichever is later, to the date of initial submission of the NDA, January 22, 2009, a period of 1533 days. One-half of this period is 766.5 days. According to MPEP § 2758, "half days will be ignored and thus will not be subtracted from the regulatory review period." Thus, the 2259-day period is reduced by 766 days, resulting in a revised regulatory period of 1493 days.

Pursuant to 35 U.S.C. § 156(c)(3) and 37 C.F.R. § 1.775(d)(2-4), if the period remaining in the term of the patent after the date of approval January 18, 2011 to June 22, 2019, a period of 3077 days, when added to the revised regulatory period (1493 days) exceeds 14 years (5113 days), the period of extension must be reduced so that the total of both such periods

does not exceed fourteen years. In this case, the total of both such periods does not exceed fourteen years and, therefore, the 1493-day revised regulatory review period is not reduced.

The period of patent term extension as calculated above is also subject to the provisions of 35 U.S.C. § 156(g)(6) and 37 C.F.R. § 1.775(d)(5). U.S. Patent No. 6,063,771 issued after the enactment of the statute, September 24, 1984 and, thus, the five-year maximum on extension as provided in 35 U.S.C. § 1.56(g)(6) and 37 C.F.R. § 1.775(d)(5) is applicable. Since this maximum is greater than the period calculated above, the term of the patent is eligible for a 1493-day extension until July 24, 2023.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner for Patents and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (*see* § 1.765):

Applicant acknowledges a duty to disclose to the Commission for Patents and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought. Applicant is unaware of any such information other than that already presented in this application and attached Exhibits.

(14) The prescribed fee for receiving and acting upon the application for extension (see § 1.20(j)):

As indicated by the letter of transmittal submitted with this application, the Commissioner for Patents has been authorized to charge the filing fee of $1,120.00 and any additional fees which may be required by this or any other related paper, or credit any overpayment to Deposit Account No. 05-0840 in the name of Eli Lilly and Company and any additional fees which may be required.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

James J. Sales
Barnes & Thornburg LLP
11 S. Meridian Street
Indianapolis, IN 46204
(317) 231-6423

****

Pursuant to 37 C.F.R. § 1.740(b) and MPEP § 2753, two additional copies of this application (for a total of three copies) are submitted herewith.

As the undersigned agent of Lilly, the owner of record of U.S. Patent No. 6,342,482, which, by submission of this paper and attached Exhibits, now applies for an extension of term of this patent, I, James J. Sales, declare that (1) I am a Patent Attorney authorized to practice before the Patent and Trademark Office and have general authority from Lilly to act on its behalf on at least this patent matter; that (2) I have reviewed and understand the contents of this application for extension of U.S. Patent No. 6,342,482; that (3) I believe the patent is subject to extension pursuant to 37 C.F.R. § 1.714; that (4) I believe the length of extension claimed is fully justified under 35 U.S.C. § 156 and applicable regulations; and that (5) I believe the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent extension issuing thereon.

Respectfully submitted,

/James J. Sales/
James J. Sales
Attorney Reg. No. 33,773

EXHIBIT A

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 1

Patent #: 6063771 **Issue Dt:** 05/16/2000 **Application #:** 09338116 **Filing Dt:** 06/22/1999

Inventor: DANIEL EARL SNYDER

Title: FORMULATIONS FOR CONTROLLING HUMAN LICE

Assignment: 1

Reel/Frame: 010056/0605 **Recorded:** 06/22/1999 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: SNYDER, DANIEL EARL **Exec Dt:** 06/18/1999

Assignee: ELI LILLY AND COMPANY
PATENT DIVISION
LILLY CORPORATE CENTER
INDIANAPOLIS, INDIANA 46285

Correspondent: ELI LILLY AND COMPANY
CHERYL EYED
LILLY CORPORATE CENTER
INDIANAPOLIS, IN 46285

Search Results as of: 03/02/2011 05:17 PM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350. v.2.1
Web interface last modified: Apr 30, 2009 v.2.1

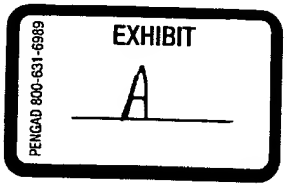


EXHIBIT B

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NATROBA Topical Suspension safely and effectively. See full prescribing information for NATROBA Topical Suspension.

Natroba (spinosad) topical suspension, 0.9%
For topical use
Initial U.S. Approval: 2011

----------INDICATIONS AND USAGE----------

NATROBA Topical Suspension is a pediculicide indicated for the topical treatment of head lice infestations in patients four (4) years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------

- For topical use only. Not for oral, ophthalmic, or intravaginal use.(2)
- Shake bottle well. (2)
- Apply product to dry scalp and hair using only the amount needed to cover the scalp and hair. (2)
- Rinse off with warm water after 10 minutes. (2)

Repeat treatment if live lice are seen 7 days after first treatment. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Suspension: 9 mg of spinosad per gram of NATROBA Topical Suspension (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Benzyl alcohol toxicity: Not recommended in infants below the age of 6 months; potential for increased systemic absorption. (5.1)

----------ADVERSE REACTIONS----------

Most common adverse events (>1%) were application site erythema and ocular erythema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ParaPRO, LLC at 1-855-628-7622 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

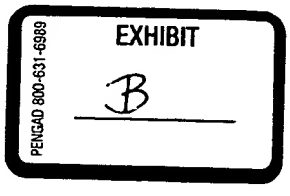
- Nursing Mothers: Caution should be exercised when administered to a nursing mother. (8.3)
- Pediatric Use: Safety in pediatric patients below the age of 4 years has not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.



FULL PRESCRIBING INFORMATION
NATROBA
(spinosad)
Topical Suspension
0.9%

1 INDICATIONS AND USAGE

1.1 Indication

NATROBA (spinosad) Topical Suspension is indicated for the topical treatment of head lice infestation in patients four (4) years of age and older.

1.2 Adjunctive Measures

NATROBA Topical Suspension should be used in the context of an overall lice management program:

- Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding and towels.
- Wash personal care items such as combs, brushes and hair clips in hot water
- A fine-tooth comb or special nit comb may be used to remove dead lice and nits.

2 DOSAGE AND ADMINISTRATION

For topical use only. NATROBA Topical Suspension is not for oral, ophthalmic, or intravaginal use.

Shake bottle well. Apply sufficient NATROBA Topical Suspension to cover dry scalp, then apply to dry hair. Depending on hair length, apply up to 120 mL (one bottle) to adequately cover scalp and hair. Leave on for 10 minutes, then thoroughly rinse off NATROBA Topical Suspension with warm water. If live lice are seen 7 days after the first treatment, a second treatment should be applied. Avoid contact with eyes.

3 DOSAGE FORMS AND STRENGTHS

0.9%, viscous, slightly opaque, light orange-colored suspension.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Benzyl Alcohol Toxicity

NATROBA Topical Suspension contains benzyl alcohol and is not recommended for use in neonates and infants below the age of 6 months. Systemic exposure to benzyl alcohol has been associated with serious adverse reactions and death in neonates and low birth-weight infants *[See Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

NATROBA Topical Suspension was studied in two randomized, active-controlled trials (N=552) in subjects with head lice; the results are presented in Table 1.

Table 1: Selected Adverse Events Occurring in at least 1% of Subjects

Signs	Spinosad (N=552)	Permethrin 1% (N=457)
Application site erythema	17(3%)	31(7%)
Ocular erythema	12 (2%)	15 (3%)
Application site irritation	5 (1%)	7 (2%)

Other less common reactions (less than 1% but more than 0.1%) were application site dryness, application site exfoliation, alopecia, and dry skin.

Systemic safety was not assessed in pediatric subjects under 4 years of age as laboratory parameters were not monitored in these controlled studies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

There are no adequate and well-controlled studies with NATROBA Topical Suspension in pregnant women. Studies in humans did not assess for the absorption of benzyl alcohol contained in NATROBA Topical Suspension. Reproduction studies conducted in rats and rabbits were negative for teratogenic effects. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

No comparisons of animal exposure with human exposure are provided in this labeling due to the low systemic exposure noted in the clinical pharmacokinetic study *[see Clinical Pharmacology (12.3)]* which did not allow for the determination of human AUC values that could be used for this calculation.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 10, 50 and 200 mg/kg/day spinosad were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. No teratogenic effects were noted at any dose. Maternal toxicity occurred at 200 mg/kg/day. Oral doses of 2.5, 10, and 50 mg/kg/day spinosad were administered during the period of organogenesis (gestational days 7 – 19) to pregnant female rabbits. No teratogenic effects were noted at any dose. Maternal toxicity occurred at 50 mg/kg/day.

A two-generation dietary reproduction study was conducted in rats. Oral doses of 3, 10, and 100 mg/kg/day spinosad were administered to male and female rats from 10-12 weeks prior to mating and throughout mating, parturition, and lactation. No reproductive/developmental toxicity was noted at doses up to 10 mg/kg/day. In the presence of maternal toxicity, increased dystocia in parturition, decreased gestation survival, decreased litter size, decreased pup body weight, and decreased neonatal survival occurred at a dose of 100 mg/kg/day.

8.3 Nursing Mothers

Spinosad, the active ingredient in NATROBA Topical Suspension is not systemically absorbed; and therefore, will not be present in human milk. However, NATROBA Topical Suspension contains benzyl alcohol, which may be systemically absorbed through the skin, and the amount of benzyl alcohol excreted in human milk with use of NATROBA Topical Suspension is unknown. Caution should be exercised when NATROBA Topical Suspension is administered to a lactating woman. A lactating woman may choose to pump and discard breast milk for 8 hours (5 half-lives of benzyl alcohol) after use to avoid infant ingestion of benzyl alcohol.

8.4 Pediatric Use

The safety and effectiveness of NATROBA Topical Suspension have been established in pediatric patients 4 years of age and older with active head lice infestation *[see Clinical Studies (14)]*.

Safety in pediatric patients below the age of 4 years has not been established. NATROBA Topical Suspension is not recommended in pediatric patients below the age of 6 months because of the potential for increased systemic absorption due to

a high ratio of skin surface area to body mass and the potential for an immature skin barrier.

NATROBA Topical Suspension contains benzyl alcohol which has been associated with serious adverse reactions and death in neonates and low birth-weight infants. The "gasping syndrome" (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birthweight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants, as well as patients receiving high dosages, may be more likely to develop toxicity *[see Warning and Precautions (5.1)]*.

8.5 Geriatric Use

Clinical studies of NATROBA Topical Suspension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

10 OVERDOSAGE

If oral ingestion occurs, seek medical advice immediately.

11 DESCRIPTION

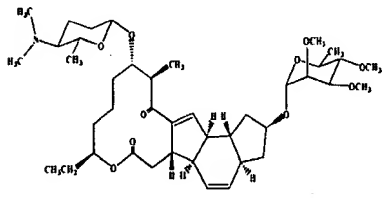
NATROBA (spinosad) Topical Suspension, is a slightly opaque, light orange colored, viscous topical suspension.

Spinosad, the active ingredient, is derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa*.

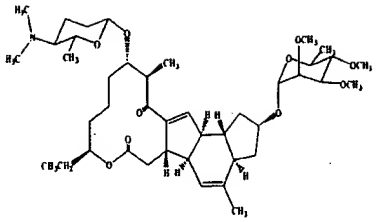
Spinosad is a mixture of spinosyn A and spinosyn D in a ratio of approximately 5 to 1 (spinosyn A to spinosyn D).

Spinosyn A: The chemical name is: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,a5-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino) tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-metyl-, (2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-

Spinosyn D: The chemical name is: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino) tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimetyl-, (2S,3aSR,5aS,5bS,9S,13S,14R,16aS,16bS)-



Spinosyn A ($C_{41}H_{65}NO_{10}$)
MW 731.461



Spinosyn D ($C_{42}H_{67}NO_{10}$)
MW 745.477

NATROBA Topical Suspension contains 9 mg spinosad per gram in a viscous, slightly opaque, light orange colored vehicle consisting of Water, Isopropyl Alcohol, Benzyl Alcohol, Hexylene Glycol, Propylene Glycol, Cetearyl Alcohol, Stearalkonium Chloride, Ceteareth-20, Hydroxyethyl Cellulose, Butylated Hydroxytoluene, FD&C Yellow #6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Spinosad causes neuronal excitation in insects. After periods of hyperexcitation, lice become paralyzed and die.

12.2 Pharmacodynamics

The pharmacodynamics of NATROBA Topical Suspension has not been studied.

12.3 Pharmacokinetics

An open-label, single-center study was conducted over a period of seven days to determine the pharmacokinetic profile of spinosad 1.8% in pediatric subjects with head lice infestation. Fourteen (14) subjects, 4 – 15 years of age, with head lice were enrolled into the study. All subjects applied a single topical (scalp) treatment of spinosad 1.8% for 10 minutes, after which the test article was washed off, and subjects underwent plasma sampling. Plasma samples were analyzed by a validated LC/MS/MS method. Results demonstrated that spinosad was below the limit of quantitation (3ng/mL) in all samples. The bioavailability of benzyl alcohol from NATROBA Topical Suspension is unknown as plasma concentrations of benzyl alcohol were not determined in these subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of fertility

In an oral (diet) mouse carcinogenicity study, spinosad was administered to CD-1 mice at doses of 0.0025, 0.008, and 0.036% in the diet (approximately 3.4, 11.4, and 50.9 mg/kg/day for males and 4.2, 13.8, and 67.0 mg/kg/day for females) for 18 months. No treatment-related tumors were noted in the mouse carcinogenicity study up to the highest doses evaluated in this study of 50.9 mg/kg/day in male mice and 13.8 mg/kg/day in female mice. Female mice treated with a dose of 67.0 mg/kg/day were not evaluated in this study due to high mortality.

In an oral (diet) rat carcinogenicity study, spinosad was administered to Fischer 344 rats at doses of 0.005, 0.02, 0.05, and 0.1% in the diet (approximately 2.4, 9.5, 24.1 and 49.4 mg/kg/day for males and 3.0, 12.0, 30.1 and 62.8 mg/kg/day for females) for 24 months. No treatment-related tumors were noted in the rat carcinogenicity study in male or female rats up to the highest doses evaluated in this study of 24.1 mg/kg/day in male rats and 30.1 mg/kg/day in female rats. Rats in the highest dose group in this study were not evaluated due to high mortality.

Spinosad demonstrated no evidence of mutagenic or clastogenic potential based on the results of four *in vitro* genotoxicity tests (Ames assay, mouse lymphoma L5178Y assay, Chinese hamster ovary cell chromosome aberration assay, and rat hepatocyte unscheduled DNA synthesis assay) and one *in vivo* genotoxicity test (mouse bone marrow micronucleus assay).

Oral administration of spinosad (in diet) to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 10 mg/kg/day *[see Pregnancy (8.1)]*.

14 CLINICAL STUDIES

Two multicenter, randomized, investigator-blind, active-controlled studies were conducted in 1038 subjects 6 months of age and older with head lice infestation. A total of 552 subjects were treated with NATROBA Topical Suspension. For the evaluation of efficacy, the youngest subject from each household was considered to be the primary subject of the household, and other members in the household were enrolled in the study as secondary subjects, and evaluated for all safety parameters.

In Study 1, 91 primary subjects were randomized to NATROBA Topical Suspension, and 89 primary subjects were randomized to permethrin 1%. In Study 2, 83 and 84 primary subjects were randomized to NATROBA Topical Suspension and permethrin 1%, respectively.

In both studies, all subjects who were treated on Day 0 returned for efficacy evaluation at Day 7. Subjects with live lice present at Day 7 received a second treatment. Subjects who were lice free on Day 7 were to return on Day 14 for evaluation. Subjects with live lice and who received a second treatment were to return on Days 14 and 21.

Efficacy was assessed as the proportion of primary subjects who were free of live lice 14 days after the final treatment. Table 2 contains the proportion of primary subjects who were free of live lice in each of the two trials.

Table 2. Proportion of Subjects Free of Live Lice 14 days After Last Treatment

Study 1		Study 2	
Natroba N=91	permethrin 1% N=89	Natroba N=83	permethtrin 1% N=84
77 (84.6%)	40 (44.9%)	72 (86.7%)	36 (42.9%)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NATROBA (spinosad) Topical Suspension, 0.9% is a slightly opaque, light orange colored, viscous liquid, supplied in 4 oz (120 mL) high density polyetheylene (HDPE) bottles. NDC 52246-929-04

16.2 Storage and Handling

- Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).
- Keep out of reach of children

17 PATIENT COUNSELING/INFORMATION

[See FDA-approved patient labeling (Patient Information)]

The patient should be instructed as follows:

- Shake bottle well immediately prior to use
- Use NATROBA Topical Suspension only on dry scalp and dry scalp hair.
- Do not swallow.
- Avoid contact with eyes. If NATROBA Topical Suspension gets in or near the eyes, rinse thoroughly with water.
- Wash hands after applying NATROBA Topical Suspension
- Use NATROBA Topical Suspension on children only under direct supervision of an adult.
- If pregnant or breastfeeding, consult a physician before use.

Patient Information

Natroba™ (Nah-TRO-buh) (spinosad) Topical Suspension, 0.9%

Important: For use on scalp hair and scalp only. Do not get NATROBA Topical Suspension in your eyes, mouth, or vagina.

Read the Patient Information that comes with NATROBA Topical Suspension before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is NATROBA Topical Suspension?

NATROBA Topical Suspension is a prescription medicine used to get rid of lice in scalp hair of children and adults.

It is not known if NATROBA Topical Suspension is safe for children under 4 years of age or in people over age 65.

Once NATROBA Topical Suspension is washed off, a fine-tooth comb may be used to remove treated lice and nits from the hair and scalp, but combing is not required. All personal items exposed to the hair or lice should be washed in hot water or dry-cleaned. See "How do I stop the spread of lice?" at the end of this leaflet.

What should I tell my healthcare provider before I use NATROBA Topical Suspension?

Tell your healthcare provider about all of your medical conditions, or the medical conditions of your child, including if you or your child:

- have any skin conditions or sensitivities
- are pregnant or planning to become pregnant. It is not known if NATROBA Topical Suspension can harm your unborn baby.
- are breastfeeding. Talk to your health care provider if you are breastfeeding.

How should I use NATROBA Topical Suspension?

- Use NATROBA Topical Suspension exactly as prescribed. Your healthcare provider will prescribe the treatment that is right for you. Do not change your treatment unless you talk to your healthcare provider.
- Use NATROBA Topical Suspension in one or two treatments that are one week apart. If live lice are seen one week (7 days) after you first used NATROBA Topical Suspension you will need to use NATROBA Topical Suspension again.
- Shake bottle well right before use.
- Use NATROBA Topical Suspension when your hair is dry. Do not wet your hair before applying NATROBA Topical Suspension.
- It is important to use enough NATROBA Topical Suspension to coat completely every single louse and to leave it on your scalp for the full 10 minutes. See the detailed Patient Instructions for Use at the end of this leaflet.
- Because you need to completely cover all of the lice with NATROBA Topical Suspension, you may need help in applying NATROBA Topical Suspension to your scalp and hair. Make sure that you and anyone who helps you apply NATROBA Topical Suspension reads and understands this leaflet and the Patient Instructions for Use.

- Children will need an adult to apply NATROBA Topical Suspension for them.
- Do not swallow NATROBA Topical Suspension. If swallowed, call your healthcare provider right away.
- Do not get into eyes. If NATROBA Topical Suspension gets in the eye, flush with water right away.
- Wash your hands after you apply NATROBA Topical Suspension.

What are the possible side effects of NATROBA Topical Suspension?

People using NATROBA Topical Suspension may have skin or eye:

- Redness
- Irritation

If skin or eye irritation happens, rinse with water right away, then call your healthcare provider or go to the emergency department

These are not all the side effects of NATROBA Topical Suspension. For more information, ask your healthcare provider.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NATROBA Topical Suspension?

- Store NATROBA in a dry place at room temperature, 20°C to 25°C (68° F to 77° F).

Keep NATROBA Topical Suspension and all medicines out of the reach of children.

What are the ingredients in NATROBA Topical Suspension?

Active ingredient: spinosad
Inactive ingredients: water, isopropyl alcohol, benzyl alcohol, hexaylene glycol, propylene glycol, cetearyl alcohol, stearalkonium chloride, ceteareth-20, hydroxyethyl cellulose, butylated hydroxytoluene, FD&C yellow #6

General Information about NATROBA Topical Suspension

Medicines are sometimes prescribed for conditions other than those described in the patient information leaflets. Do not use NATROBA Topical Suspension for any condition for which it was not prescribed by your healthcare provider. Do not give NATROBA to other people, even if they have the same symptoms as you. It may harm them.

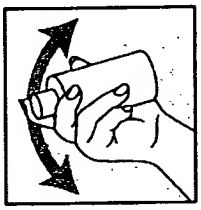
This leaflet summarizes the most important information about NATROBA Topical Suspension. If you would like more information, talk to your healthcare provider. You can also ask your healthcare provider for information about NATROBA Topical Suspension that is written for healthcare professionals.

Patient Instructions for Use

Completely cover the scalp with NATROBA Topical Suspension. Lice and nits live near the scalp. Use as much product as needed to completely cover the scalp first, and then apply outwards towards the ends of the hair.

For very thick, medium length hair or long hair, an entire bottle (120mL) of NATROBA Topical Suspension may be needed to cover the scalp and hair. Less NATROBA Topical Suspension may be needed for shorter, thinner hair.

Step 1

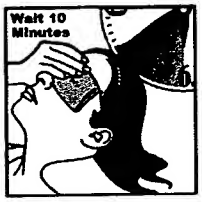


- Shake NATROBA Topical Suspension bottle well right before use.

Step 2

- Cover your face and eyes with a towel and keep your eyes closed tightly.
- Apply NATROBA Topical Suspension directly to **dry** hair.
- Completely cover the scalp first, and then apply outwards towards the ends of the hair.
- If not enough NATROBA Topical Suspension is used, some lice may escape treatment. It is important to use enough NATROBA Topical Suspension to cover your entire scalp and all scalp hair.

Step 3



- Allow NATROBA Topical Suspension to stay on your hair for 10 minutes. Use a timer or clock and start timing after you have completely covered your hair and scalp with NATROBA Topical Suspension.
- Continue to keep eyes covered to prevent dripping into your eyes.
- After 10 minutes, completely rinse NATROBA Topical Suspension from your hair and scalp with warm water.
- You or anyone who helps you apply NATROBA Topical Suspension should wash hands after application.
- It is okay to shampoo your hair any time after the treatment.

One week (7 days) after your first treatment, if live lice are seen, repeat the steps above.

How do I stop the spread of lice?

To help prevent the spread of lice from one person to another, here are some steps you can take:

- Avoid direct head-to-head contact with anyone known to have live, crawling lice.
- Do not share combs, brushes, hats, scarves, bandannas, ribbons, barrettes, hair bands, towels, helmets, or other hair-related personal items with anyone else, whether they have lice or not.
- Avoid sleepovers and slumber parties during lice outbreaks. Lice can live in bedding, pillows, and carpets that have recently been used by someone with lice.
- After finishing treatment with lice medicine, check everyone in your family for lice after one week. Be sure to talk to your healthcare provider about treatments for those who have lice.
- Machine-wash any bedding and clothing used by anyone having lice. Machine wash at high temperatures (150°F) and tumble in a hot dryer for 20 minutes.

This patient Leaflet has been approved by the U.S. Food and Drug Administration.

MANUFACTURED FOR:
ParaPRO LLC
Carmel, IN 46032

DISTRIBUTED BY:
ParaPRO and/or Pernix Therapeutics, Inc.
Magnolia, TX 77354

NAT-PI-000 Effective Date: 18JAN2011

EXHIBIT C

US006342482B1

(12) **United States Patent**
Snyder

(10) **Patent No.: US 6,342,482 B1**
(45) **Date of Patent: *Jan. 29, 2002**

(54) **FORMULATIONS FOR CONTROLLING HUMAN LICE**

(75) Inventor: **Daniel Earl Snyder**, Indianapolis, IN (US)

(73) Assignee: **Eli Lilly and Company**, Indianapolis, IN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/543,441**

(22) Filed: **Apr. 5, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/338,116, filed on Jun. 22, 1999, now Pat. No. 6,063,771.
(60) Provisional application No. 60/091,658, filed on Jul. 2, 1998.

(51) **Int. Cl.**[7] **A61K 31/76**
(52) **U.S. Cl.** **514/31**; 514/880
(58) **Field of Search** 514/31

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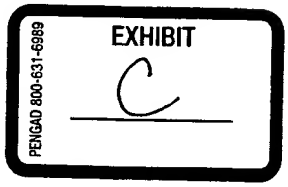
Primary Examiner—Rebecca Cook
(74) *Attorney, Agent, or Firm*—John C. Demeter

(57) **ABSTRACT**

Safer pediculicidal formulations comprising a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier, and methods of controlling lice infestations in a human with these formulations are provided.

12 Claims, No Drawings



FORMULATIONS FOR CONTROLLING HUMAN LICE

CROSS REFERENCE

This application is a continuation of application Ser. No. 09/338,116, filed Jun. 22, 1999 now U.S. Pat. No. 6,063,771, which claims priority of Provisional Application Ser. No. 60/091,658 filed Jul. 2, 1998.

BACKGROUND OF THE INVENTION

Infestation of the human body by lice is an increasingly prevalent social and health problem in many countries, including the United States. Lice are very small insects (about 2–3 mm in length). They deposit eggs either on a hair or fabric fiber and attach them firmly with a cementlike excretion. The eggs generally hatch in about six to ten days, depending on temperature. The empty shells remaining after the nymphs emerge from the eggs look like white grains of sand. These shells are called nits.

The Anoplura, or sucking lice, are parasites found on nearly all groups of mammals. Of the 15 recognized families of Anoplura, two families, Pediculidae and Pthiridae, have species found on humans. *Pediculus humanus* is the only species in the family Pediculidae that infests humans. It includes the head louse, *Pediculus humanus capitis;* and the body or clothing louse, *Pediculus humanus humanus,* sometimes called *Pediculus corporis.* The crab louse, *Pthirus pubis,* is a distinct species and is the only member of the family Pthiridae that infests humans. As used herein, the term "human lice or louse" includes a member of *Pediculus humanus* or *Pthirus pubis.*

Human lice are spread by crowding and common usage of clothing and combs. Initially, infestations result at most in irritation, but the irritation can lead to infection of the irritated area. There are at least three major diseases that are primarily transmitted by lice: epidemic typhus, trench fever and relapsing fever.

Although the human lice varieties are related, each of them has specific characteristics with regard to habitat and feeding. For example, head lice are small hard-shelled ectoparasites which cling to hair shafts while feeding, mating and laying eggs. The louse must remain on the head or it will die within a short period of time. Head lice proliferate at an incredible rate. A louse is ready to mate and reproduce within 10 hours after hatching. Under ideal conditions, a female louse may produce up to 300 eggs in its lifetime. Ideal conditions include an adequate food supply, environmental temperatures from about 28° C. to about 32° C., and relative humidity of about 70% to about 90%.

Poor hygienic and grooming habits are also known to contribute significantly to the spread of lice. Thus, lice infestations are most serious in geographical areas where the inhabitants have both substandard hygienic facilities and practices. Lice can be a problem, however, even when conditions are relatively sanitary.

The louse's hard chitinous exoskeleton serves as protection from external elements. Lice eggs (or ova) are similarly protected by a chitinous sheath surrounding the eggs and attached to the hair shaft. Although lice may be affected by the use of an insecticide, the eggs often remain resistant to attack. Thus, optimum treatment of a lice infestation includes both a pediculicide, which kills the adult lice, and an ovicide, which interrupts the development of the eggs.

Biologically active agents have been used for some time in attempts to control lice. For example, lindane (gammabenzene hexachloride), organophosphates (malathion), natural pyrethrins, and synthetic compounds known as pyrethroids (such as permethrin) have been used as pediculicides in lice treatment formulations. These agents however, have drawbacks. For example, lindane has a poor safety profile, and lice have developed resistance to it. Natural pyrethrin requires frequent follow-up treatments because it provides only short term residual action. Synthetic pyrethroids, although more effective against lice than natural pediculicides, are often more toxic to the subject being treated.

Spinosyns (also known as A83453 factors) are agricultural insecticides that have shown activity against 1) southern armyworm and other insects in the order Lepidoptera, 2) cotton aphid and other members of the order Homoptera, and 3) stable flies, blow flies and mosquitos, which are members of the insect order Diptera. (See U.S. Pat. No. 5,362,634, infra). Spinosyn A has an excellent human and animal safety and toxicological profile.

This invention provides formulations for controlling infestations of lice in a human comprising a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier. It also provides methods of using these formulations to control human lice species. These formulations and methods control lice in a safer, more effective manner than previously known anti-lice formulations and methods.

SUMMARY OF THE INVENTION

This invention relates to formulations for controlling a lice infestation in a human comprising a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier. The invention further relates to methods of controlling a lice infestation in a human comprising topically administering to the human an amount of a spinosyn, or a physiologically acceptable derivative/salt thereof, that controls the lice. The formulations and methods of this invention are safer and more effective than those presently available. A particular benefit of these formulations is their effectiveness against louse species that have become resistant to currently used products. Preferred formulations and methods of this invention are hair care formulations, such as shampoos, lotions and conditioners, and methods of using these hair care formulations for controlling a lice infestation in a human.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides pediculicidal/ovicidal (anti-lice) formulations for controlling a lice infestation in a human comprising as an active ingredient a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier. Especially useful formulations of this invention are hair-care formulations. Especially useful hair-care formulations are shampoos.

This invention also provides methods for controlling a lice infestation in a human comprising topically administering a formulation comprising a spinosyn or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier. In another aspect this invention provides the use of a spinosyn, or a physiologically acceptable derivative or salt thereof, or a formulation containing either an spinosyn or derivative or salt thereof, for the manufacture of a medicament for controlling lice in a human.

The term "controlling a lice infestation" refers to treating an active lice infestation or preventing an infestation in a human who is likely to be exposed to a lice infestation.

Spinosyns are naturally derived fermentation products. They are macrolides produced by cultivation of *Saccharopolyspora spinosa*. The fermentation produces multifactors, including spinosyn A and spinosyn D (also called A83543A and A83543D). Spinosyn A and spinosyn D are the two spinosyns that are most active as insecticides. A product comprised mainly of these two spinosyns (approximately 85% A and 15% D) is available commercially from Dow Agrosciences under the name spinosad. The name "spinosad" comes from a contraction of the spinosyns "A" and "D".

Each spinosyn has a 12-membered macrocyclic ring that is part of an unusual tetracyclic ring system to which two different sugars are attached, the amino-sugar forosamine and the neutral sugar 2N, 3N, 4N-tri-O-methylrhamnose. This unique structure sets the spinosyns apart from other macrocyclic compounds.

Spinosyn A (A83543A) was the first spinosyn isolated and identified from the fermentation broth of *Saccharapolyspora spinosa*. Subsequent examination of the fermentation broth revealed that the parent strain of *S. spinosa* produced a number of spinosyns that have been labeled A to J (A83543A to J). Compared to spinosyn A, spinosyns B–J are characterized by differences in the substitution patterns on the amino group of the forosamine, at selected sites on the tetracyclic ring system and on 2N, 3N, 4N-tri-O-methylrhamnose. The strains of *S. spinosa* currently in use produce a mixture of spinosyns of which the primary components are spinosyn A (~85%) and spinosyn D (~15%). Additional spinosyns, lettered from K to W, have been identified from mutant strains of *S. spinosa*.

The term "spinosyn or a derivative thereof" as used herein refers to an individual spinosyn factor (A, B, C, D, E, F, G, H, J, K, L, M, N, O, P, Q, R, S, T, U, V, W or Y), an N-demethyl derivative of an individual spinosyn factor, or a combination thereof. For convenience, the term "spinosyn component" will also be used herein to mean an individual spinosyn, or a physiologically acceptable derivative or salt thereof, or a combination thereof.

Boeck et al. described spinosyns A–H and J (which they called A83543 factors A, B, C, D, E, F, G, H and J), and salts thereof, in U.S. Pat. No. 5,362,634 (issued Nov. 8, 1994); U.S. Pat. No. 5,496,932 (issued Mar. 5, 1996); and U.S. Pat. No. 5,571,901 (issued Nov. 5, 1996). Mynderse et al. described spinosyns L–N (which they called A83543 factors L, M and N), their N-demethyl derivatives, and salts thereof, in U.S. Pat. No. 5,202,242 (issued Apr. 13, 1993); and Turner et al. described spinosyns Q–T (which they called A83543 factors Q, R, S and T), their N-demethyl derivatives, and salts thereof, in U.S. Pat. No. 5,591,606 (issued Jan. 7, 1997) and U.S. Pat. No. 5,631,155 (issued May 29, 1997). These patents are incorporated herein by reference. Spinosyns K, O, P, U, V, W and Y are described, for example, by Carl V. DeAmicis, James E. Dripps, Chris J. Hatton and Laura I. Karr in American Chemical Society's Symposium Series: Phytochemicals for Pest Control, Chapter 11, "Physical and Biological Properties of Spinosyns: Novel Macrolide Pest-Control Agents from Fermentation", pages 146–154 (1997).

The spinosyns can react to form salts. Salts that are physiolocally acceptable are also useful in the formulations and methods of this invention. The salts are prepared using standard procedures for salt preparation. For example, spinosyn A can be neutralized with an appropriate acid to form an acid additional salt. The acid addition salts of spinosyns are particualrly useful. Representative suitable acid addition salts include salts formed by reaction with either an organic or inorganic acid such as, for example, sulfuric, hydrochloric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, cholic, pamoic, mucic, glutamic, camphoric, glutaric, glycolic, phthalic, tartaric, formic, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic and like acids.

In addition to the spinosyn component, the formulations of this invention may further include one or more other compounds that have activity against lice such as, for example, synthetic pyrethroids, natural pyrethins, and lindane. All ratios, percentages, and parts discussed herein are "by weight" unless otherwise specified.

Pediculicidal/Ovicidal Formulations

The anti-lice formulations of this invention may be formulated in a number of ways. Particularly useful formulations are shampoos, conditioners, and lotions. These formulations optionally also comprise one or more of the following: a) a surfactant; b) from about 1% to about 10% of a non-volatile silicone material; and/or c) from about 0.5% to about 5% of a suspending agent.

I. Shampoos

The shampoo formulations of this invention comprise a spinosyn, or a physiologically acceptable derivative or salt thereof, together with water, a surfactant, and an amide and may optionally comprise another anti-lice agent, a silicone compound, a suspending agent and other cosmetically acceptable components.

Human hair becomes soiled due to contact with the surrounding atmosphere and the build up of sebum secreted by the head. When the hair is soiled, it has a dirty feel and an unattractive appearance. The shampoo formulations of this invention both clean the hair and effectively control a lice infestation.

A. Spinosyn Component

When used in a shampoo formulation, the spinosyn component is present at a level of from about 0.1% to about 30%, preferably from about 1% to about 10%.

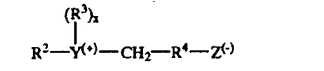
B. Surfactants

Surfactants suitable for use in these formulations can be any of a wide variety of synthetic anionic, amphoteric, zwitterionic and non-ionic surfactants. Surfactants are generally present in shampoo formulations at a level of from about 5% to about 30%, preferably from about 15% to about 25%.

Examples of synthetic anionic surfactants are the alkali metal salts of organic sulfuric reaction products having an alkyl radical containing from 8–22 carbon atoms and a sulfonic acid or sulfuric acid ester radical (included in the term alkyl is the alkyl portion of higher acyl radicals). Sodium, ammonium, potassium or triethanolamine alkyl sulfates are preferred, especially those obtained by sulfating the higher alcohols (C_8–C_{18} carbon atoms); sodium coconut oil fatty acid monoglyceride sulfates and sulfonates; sodium or potassium salts of sulfuric acid esters of the reaction product of 1 mole of a higher fatty alcohol (e.g., tallow or coconut oil alcohols) and 1 to 12 moles of ethylene oxide; sodium or potassium salts of alkyl phenol ethylene oxide ether sulfate with 1 to 10 units of ethylene oxide per molecule and in which the alkyl radicals contain from 8 to 12 carbon atoms; sodium alkyl glyceryl ether sulfonates; the reaction product of fatty acids having from 10 to 22 carbon atoms esterified with isethionic acid and neutralized with sodium hydroxide; and water soluble salts of condensation products of fatty acids with sarcosine.

Examples of zwitterionic surfactants are derivatives of aliphatic quaternary ammonium, phosphonium, and sulfo-

nium compounds, in which the aliphatic radicals can be straight or branched, and wherein one of the aliphatic substituents contains from about 8 to 18 carbon atoms and one contains an anionic water-solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate, or phosphonate. A general formula for these compounds is:



wherein R^2 contains an alkyl, alkenyl, or hydroxyalkyl radical of from about 8 to about 18 carbon atoms, from 0 to about 10 ethylene oxide moieties and from 0 to 1 glyceryl moiety; Y is a nitrogen, phosphorus, or sulfur atom; $R^3$is an alkyl or monohydroxyalkyl group containing 1 to about 3 carbon atoms; x is 1 when Y is sulfur and 2 when Y is nitrogen or phosphorus; R^4 is alkylene or hydroxyalkylene of from 1 to about 4 carbon atoms, and Z is a carboxylate, sulfonate, sulfate, phosphonate, or phosphate radical.

Examples include:

4-[N,N-di(2-hydroxyethyl)-N-octadecylammonio]-butane-1-carboxylate;

5-[S-3-hydroxypropyl-S-hexadecylsulfonio]-3-hydroxypentane-1-sulfate;

3-[P,P-diethyl-P-3,6,9-trioxatetradexocylphosphonio]-2-hydroxypropane-1-phosphate;

3-[N,N-dipropyl-N-3-dodecoxy-2-hydroxypropylammonio]-propane-1-phosphate;

3-(N,N-dimethyl-N-hexadecylammonio)propane-1-sulfonate;

3-(N,N-dimethyl-N-hexadecylammonio)-2-hydroxy-propane-1-sulfonate;

N,N-di(2-hydroxyethyl)-N-(2-hydroxydodecyl)ammonio]-butane-1-carboxylate;

3-[S-ethyl-S-(3-dodecoxy-2-hydroxypropyl)sulfonio]-propane-1-phosphate;

3-[P,P-dimethyl-P-dodecylphosphonio]-propane-1-phosphonate; and

5-(N,N-di(3-hydroxypropyl)-N-hexadecylammonio]-2-hydroxypentane-1-sulfate.

Other zwitterionic surfactants, such as betaines, are also useful in the formulations of this invention. Examples of betaines include the higher alkyl betaines, such as coco dimethyl carboxymethyl betaine, lauryl dimethyl carboxymethyl betaine, lauryl dimethyl alpha-carboxyethyl betaine, cetyl dimethyl carboxymethyl betaine, lauryl bis-(2-hydroxyethyl)carboxymethyl betaine, stearyl bis-(2-hydroxypropyl)carboxymethyl betaine, oleyl dimethyl gamma-carboxypropyl betaine and lauryl bis-(2-hydroxypropyl) alpha-carboxyethyl betaine. The sulfobetaines may be represented by coco dimethyl sulfopropylbetaine, stearyl dimethyl sulfopropyl betaine, lauryl dimethyl sulfoethyl betaine, lauryl bis-(2-hydroxyethyl)sulfopropyl betaine, and the like. Amido betaines and amidosulfobetaines, wherein an RCONH $(CH_2)_3$ radical is attached to the nitrogen atom of the betaine, are also useful in the formulations of this invention.

Examples of amphoteric surfactants that can be used in the formulations of this invention are those which are derivatives of aliphatic secondary or tertiary amines in which the aliphatic radical is straight or branched and wherein one of the aliphatic substituents contains from about 8 to about 18 carbon atoms and one contains an anionic water solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate, or phosphonate. Examples of amphoteric surfactants are sodium 3-dodecylaminopropionate, sodium 3-dodecylaminopropane sulfonate, N-alkyltaurines such as the one prepared by reacting N-dodecylamine with sodium isethionate (see U.S. Pat. No. 2,658,072, Example 3), N-higher alkyl aspartic acids (see U.S Pat. No. 2,438,091), and products sold under the trade name "Miranol" and described in U.S. Pat. No. 2,528,378.

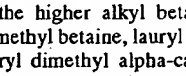
Nonionic surfactants, which are preferably used in combination with an anionic, amphoteric or zwitterionic surfactant, are compounds produced by the condensation of alkylene oxide groups (hydrophilic in nature) with an organic hydrophobic compound, which may be aliphatic or alkyl aromatic in nature. Examples of nonionic surfactants include:

1. Polyethylene oxide condensates of alkyl phenols, e.g., the condensation products of alkyl phenols having an alkyl group containing from about 6 to 12 carbon atoms in either a straight or branched chain configuration, with ethylene oxide, the ethylene oxide being present in amounts equal to 10 to 60 moles of ethylene oxide per mole of alkyl phenol. The alkyl substituent in these compounds may be derived from polymerized propylene, diisobutylene, octane, or nonane, for example.

2. Condensates of ethylene oxide with a product of the reaction of propylene oxide and ethylene diamine products which may be varied in formulation depending upon the desired balance between the hydrophobic and hydrophilic elements. For example, compounds containing from about 40% to about 80% polyoxyethylene by weight and having a molecular weight of from about 5,000 to about 11,000 resulting from the reaction of ethylene oxide groups with a hydrophobic base comprising the reaction product of ethylene diamine and excess propylene oxide, and having a molecular weight on the order of 2,500 to 3,000, are satisfactory.

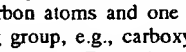
3. The condensation product of aliphatic alcohols having from 8 to 18 carbon atoms, in either straight or branched chain configuration, with ethylene oxide, e.g., a coconut alcohol ethylene oxide condensate having from 10 to 30 moles of ethylene oxide per mole of coconut alcohol, the coconut alcohol fraction having from 10 to 14 carbon atoms.

4. Long chain tertiary amine oxides corresponding to the following general formula:



wherein R_1 contains an alkyl, alkenyl, or monohydroxy alkyl radical of from about 8 to about 18 carbon atoms, from 0 to about 10 ethylene oxide moieties, and from 0 to 1 glyceryl moiety, and R_2 and R_3 contain from 1 to about 3 carbon atoms and from 0 to about 1 hydroxy group, e.g., methyl, ethyl, propyl, hydroxyethyl, or hydroxypropyl radicals. The arrow in the formula represents a semipolar bond. Examples of amine oxides suitable for use in these formulations include dimethyldodecylamine oxide, oleyldi(2-hydroxyethyl)amine oxide, dimethyloctylamine oxide, dimethyl-decylamine oxide, dimethyl-tetradecylamine oxide, 3,6,9-trioxaheptadecyldiethylamine oxide, di(2-hydroxyethyl)-tetradecylamine oxide, 2-dodecoxyethyldimethylamine oxide, 3-dodecoxy-2-hydroxypropyldi(3-hydroxypropyl)amine oxide, and dimethylhexadecylamine oxide.

5. Long chain tertiary phosphine oxides of the following general formula:



wherein R contains an alkyl, alkenyl or monohydroxyalkyl radical of from about 8 to 18 carbon atoms, from 0 to about 10 ethylene oxide moieties and from 0 to 1 glyceryl moiety, and R' and R" are each alkyl or monohydroxyalkyl groups containing from 1 to 3 carbon atoms. The arrow in the formula represents a semipolar bond.

Examples of suitable phosphine oxides include: dodecyldimethyl-phosphine oxide, tetradecyldimethylphosphine oxide, tetradecylmethylethylphosphine oxide, 3,6,9-trioxaoctadecyldimethylphosphine oxide, cetyldimethylphosphine oxide, 3-dodecoxy-2-hydroxypropyldi(2-hydroxyethyl)phosphine oxide, stearyldimethylphosphine oxide, cetylethylpropylphosphine oxide, oleyldiethylphosphine oxide, dodecyldiethylphosphine oxide, tetradecyldiethylphosphine oxide, dodecyldipropylphosphine oxide, dodecyldi(hydroxymethyl)phosphine oxide, dodecyldi(2-hydroxyethyl)phosphine oxide, tetradecylmethyl-2-hydroxypropylphosphine oxide, oleyldimethylphosphine oxide, 2-hydroxydodecyldimethylphosphine oxide.

6. Long chain dialkyl sulfoxides containing one short chain alkyl or hydroxyalkyl radical of 1 to 3 carbon atoms (usually methyl) and one long hydrophobic chain which contains alkyl, alkenyl, hydroxyalkyl, or keto alkyl radicals containing form about 8 to about 20 carbon atoms, from 0 to about 10 ethylene oxide moieties and from 0 to 1 glyceryl moiety. Examples include: octadecyl methyl sulfoxide, 2-ketotridecyl methyl sulfoxide, 3,6,9-trioxaoctadecyl 2-hydroxyethyl sulfoxide, dodecyl methyl sulfoxide, oleyl 3-hydroxypropyl sulfoxide, tetradecyl methyl sulfoxide, 3-methoxytridecyl methyl sulfoxide, 3-hydroxytridecyl methyl sulfoxide, and 3-hydroxy-4-dodecoxybutyl methyl sulfoxide.

Many additional nonsoap surfactants are described in *McCutcheon's Detergents and Emulsifiers,* 1998 Annual, published by M. C. Publishing Company, Inc.; McCutcheon Division, 175 Rock Rd., Glen Rock, N.J., 07425, U.S.A.

Anionic surfactants, particularly the alkyl sulfates, the ethoxylated alkyl sulfates and mixtures thereof, as well as the amido betaines, are preferred for use in the shampoo formulations of this invention.

C. Amides

Amides enhance the lathering of the formulations by emulsifying the shampoo components and the active component(s). The amides used in the present formulations can be any of the alkanolamides of fatty acids known for use in shampoos. These are generally mono- and diethanolamides of fatty acids having from about 8 to about 14 carbon atoms. Other suitable amides are those having multiple ethoxy groups such as PEG-3 lauramide.

In the shampoo formulations, the amide is generally present at a level of about 1% to about 7%, preferably from about 2% to about 5%, of the formulation. Prefered amides are coconut monoethanolamide, coconut diethanolamide, and mixtures thereof.

D. Water

The shampoo formulations of this invention also contain water. Water is typically present in the shampoos at levels of from about 50% to about 80%, preferably from about 60% to about 75%. After adding water, the relative viscosity of the formulation is generally in the range of from about 4,000 centipoise (cp) to about 25,000 cp, preferably from about 4,000 cp to about 12,000 cp, most preferably from about 4,000 cp to about 5,500 cp, measured at 1 RPM at 26.7° for 3 minutes using a Wells-Brookfield viscometer Model DV-CP-2 DVII, Model Cone CP-41. Viscosity modifiers and hydrotropes may be included to bring the formulation's viscosity within these ranges.

E. Optional Components

1. Silicone compounds may be incorporated into the shampoo formulations to condition the hair and facilitate removal of the dead lice, their eggs and nits. Non-volatile silicone materials are used at levels from about 1% to about 10% of the formulations. Examples of useful silicone compounds are disclosed in U.S. Pat. No. 5,292,504, Cardin et al., issued Mar. 8, 1994, incorporated herein by reference.

Non-volatile silicone-containing compounds are preferred and are used at levels of from about 0.1% to about 10%, preferably from about 0.25% to about 3%, by weight of the formulation. Examples of non-volatile silicones are polyalkyl siloxanes, poly alkylaryl siloxanes, polyether siloxane copolymers and mixtures thereof.

Useful polyalkyl siloxanes include, for example, polydimethyl siloxanes (PDMS) with viscosities ranging from about 5 to 15,000,000 cp at 25°. These siloxanes are available, for example, from the General Electric Company as the Viscasil series and from Dow Corning as the Dow Corning 200 series. The viscosity can be measured by means of a glass capillary viscometer as set forth in Dow Corning. Corporate Test Method CTM0004, Jul. 20, 1970.

Useful polyalkylaryl siloxanes include polymethylphenyl siloxanes having viscosities of from about 5 to about 15,000,000 cp at 25°. These siloxanes are available, for example, from the General Electric Company as SF 1075 methyl phenyl fluid or from Dow Corning as 556 Cosmetic Grade Fluid.

Useful polyether siloxane copolymers include polypropylene oxide modified polydimethylsiloxanes (available, for example, from Dow Corning as DC-1248), ethylene oxide or mixtures of ethylene oxide and propylene oxide. Water insoluble ones are most useful.

The siloxanes are able to condition the hair due to their ability to lubricate the hair, providing wet and dry combing benefits. Viscous, higher molecular weight siloxanes provide the best conditioning benefits and are, therefore, preferred. Fluids and gums of the siloxane polymers are most desirable. Siloxane polymer gums are rigid as opposed to a liquid or fluid, with high mass molecular weights of from about 200,000 to about 1,000,000 as viscosities from about 100,000 cp to about 150,000,000 cp at 25° C. Such gums are discussed in U.S. Pat. No. 5,292,504 (supra).

2. The shampoo formulations may incorporate suspending agents to improve long term stability. Useful suspending agents include fatty amphiphilic crystalline materials having needle-like or platelet structures, polymeric materials, clays, fumed metal oxides, and mixtures thereof. These agents are known in the art (see U.S. Pat. No. 5,292,504).

Suitable crystalline amphiphilic materials are those that have needle or platelet-type structures. Such comounds include long chain (C_{16}–C_{22}) acyl derivatives, such as ethylene glycol esters of fatty acids (e.g., ethylene glycol disterate); long chain (C_{16}–C_{22}) alkanol amides of fatty acids, such as stearamide MEA, stearyl stearate, and distearyl dithiopropionate; and mixtures thereof.

Polymeric materials that are useful as suspending agents include cross-linked polyacyclic acids (such as the Carbopol series, available from the B. F. Goodrich Chemical Company), guar gum and its derivatives, xanthan gum, cross linked copolymers of ethylene/maleic anhydrides, and mixtures thereof.

Clays and fumed metal oxides are also effective suspending agents. Examples include magnesium aluminum silicates (such as the Veegum series, available from R. T. Vanderbilt Company, Inc.), sodium aluminum silicates (such as the Laponite series, available from Laponite United

States), fumed silica, fumed alumina, fumed titania and mixtures thereof.

In the shampoo formulations of this invention suspending agents are generally present in amounts of from about 0.5% to about 5%, preferably from 0.5% to about 3%. The long chain acyl derivatives such as ethylene glycol esters of fatty acids are preferred. Most preferred is ethylene glycol distearate.

3. The shampoo formulations can also contain a variety of other components suitable for rendering the formulations more cosmetically acceptable. Such optional ingredients are known in the art and include, e.g., preservatives, such as methyl paraben, propyl paraben, methylisothiazolinone and imidazolidinyl urea; thickeners and viscosity modifiers, such as amine oxides, block polymers of ethylene oxide and propylene oxide (such as Pluronic F88 offered by BASF Wyandotte), fatty alcohols (such as cetearyl alcohol), sodium choloride, ammonium chloride, sodium sulfate, polyvinyl alcohol, propylene glycol, and ethyl alcohol; hydrotropes, such as xylene sulfonate; pH adjusting agents, such as citric acid, succinic acid, phosphoric acid, sodium hydroxide, and sodium carbonate; perfumes, dyes, quaternary ammonium compounds, such as Polyquaternium 41, sequestering agents, such as disodium ethylenediamine tetraacetate; and pearlescing agents, such as distearic acid ester of ethylene glycol, stearic acid and palmitic acid diesters of polyethylene glycol, and stearic acid monoethanolaminde. Generally, these optional components are used individually at a level of from about 0.1% to about 10% of the formulation.

The shampoo formulations of this invention are used in a conventional manner for cleaning hair. From about 10 g to about 30 g of a formulation is applied to wet hair and worked through both hair and scalp. The formulation is left on the hair and scalp for approximately 6–10 minutes and then is removed by rinsing. This process is repeated until the hair is clean.

A useful pediculicidal shampoo of this invention comprises:

(a) from about 0.1% to about 2.5% of a spinosyn, or a physiologically acceptable derivative or salt thereof;

(b) from about 5% to about 30% of a synthetic surfactant;

(c) from about 1% to about 7% of an amide; and

(d) water.

II. Hair Conditioner Formulations

The hair conditioning formulations of this invention comprise a spinosyn component and a conditioner and may optionally comprise another anti-lice agent, such as permethrin or lindane. These conditioner formulations may also be used effectively to treat a lice infestation.

Hair conditioners are products that improve the appearance, feel and manageability of hair. Conditioners are particularly important when the hair has been damaged by treatments such as permanent waving, dyeing, teasing, and bleaching, or by atmospheric conditions, such as sunlight, that cause photo-catalyzed oxidation. These factors may cause hair to have poor texture, making it difficult to manage and comb, whether wet or dry.

Conditioning products are well known and include "rinse-type" products, which are rinsed off shortly after being applied to clean hair, and "deep conditioners" which remain on the hair for extended periods of time.

A. Spinosyn Component

When used in hair conditioner formulations, the spinosyn component is present at a level of from about 0.1% to about 30%, preferably from about 1% to about 10%.

B. Conditioners

One group of conditioners useful in the hair conditioner formulations of this invention are long chain quaternary ammonium compounds combined with lipid materials, such as fatty alcohols (see U.S. Pat. No. 3,155,591, Hilfer, issued Nov. 3, 1964, and U.S. Pat. No. 4,269,824, Villamarin, et al., issued May 26, 1981). Another group of conditioners are lipids and quaternary ammonium compounds. These conditioners are used to form gel-type conditioner products having good in-use cosmetic and Theological characteristics. These types of gel-type formulations are generally described in the following documents: Barry, "The Self Bodying Action of the Mixed Emulsifer Sodium Dodecyl Sulfate/Cetyl Alcohol", *J. of Colloid and Interface Science,* 28, 82–91 (1968); Barry et al., "The Self-Bodying Action of Alkyltrimethylammonium Bromides/Cetostearyl Alcohol Mixed Emulsifiers; Influence of Quarternary Chain Length", *J. of Colloid and Interface Science,* 35, 689–708 (1971); and Barry et al., "Rheology of Systems Containing Cetomacrogo/1000-(cetostearyl alcohol), I. Self-Bodying Action", *J. of Colloid and Interface Science,* 38, 616–625 (1972).

1. Lipid Materials. The lipid materials used in these conditioners are present at a level of from about 0.5% to about 3%. These lipids are essentially water-insoluble, and contain hydrophobic and hydrophilic moieties. They include natural and synthetically-derived fatty materials selected from acids, acid derivatives, alcohols, esters, ethers, ketones, amides, and mixtures thereof, having alkyl chain lengths from about 12 to about 22 carbon atoms, preferably from 16 to 18 carbon atoms in length. Fatty alcohols and fatty esters are preferred.

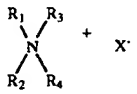
Useful fatty alcohols are known (see, for example, U.S. Pat. No. 3,155,591, supra; U.S. Pat. No. 4,165,369 (Watanabe et al., issued May 26, 1981); British Patent Specification 1,532,585, published Nov. 15, 1978; Fukushima et al., "The Effect of Cetostearyl Alcohol in Cosmetic Emulsions", *Cosmetics & Toiletries,* 98, 89–102 (1983); and Hunting, *Encyclopedia of Conditioning Rinse Ingredients,* at 204 (1987). Fatty alcohols are C_{12}–C_{16} alcohols selected from cetearyl alcohol, cetyl alcohol, isostearyl alcohol, lanolin alcohol, lauryl alcohol, oleyl alcohol, stearyl alcohol, and mixtures thereof. Preferred are cetyl alcohol, stearyl alcohol, and mixtures thereof. A particularly preferred fatty alcohol is comprised of a mixture of cetyl alcohol and stearyl alcohol containing from about 55% to about 65% (by weight of mixture) of cetyl alcohol.

Useful fatty esters are also known (see Kaufman, et al., U.S. Pat. No. 3,341,465, issued Sep. 12, 1967). Fatty esters are fatty acids in which the active hydrogen has been replaced by the alkyl group of a monohydric alcohol. The monohydric alcohols are fatty alcohols as described, supra. The fatty esters useful in these conditioner formulations include cetyl lactate, cetyl octanoate, cetyl palmitate, cetyl stearate, glyceryl monostearate, glyceryl laurate, glyceryl myristate, glyceryl oleate, glyceryl stearate, glyceryl monoacetate, and mixtures thereof. Cetyl palmitate and glycerol monostearate, or mixtures thereof, are preferred.

2. Surfactants. Cationic surfactants may be used in these conditioning formulations, either singly or in combination, generally at a level of from about 0.1% to about 5% of the final formulation. These surfactants contain amino or quaternary ammonium hydrophilic moieties that are positively charged when dissolved in the aqueous formulations of this invention. These cationic surfactants are known in the art (see McCutcheon's Detergents & Emulsifiers, supra; Schwartz et al., Surface Active Agents, Their Chemistry and

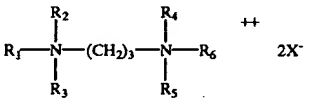
Technology, New York: Interscience Publishers, 1949; U.S. Pat. No. 3,155,591, supra; U.S. Pat. No. 3,929,678 (Laughlin et al., issued Dec. 30, 1975); U.S. Pat. No. 3,959,461 (Bailey et al., issued May 25, 1976); and U.S. Pat. No. 4,387,090 (Bolich, Jr., issued Jun. 7, 1983).

Useful quaternary ammonium cationic surfactant materials are those of the general formula:



wherein R_1 is hydrogen, an aliphatic group of from 1 to 22 carbon atoms, or an aromatic, aryl or alkylaryl group having from 12 to 22 carbon atoms; R_2 is an aliphatic group having from 1 to 22 atoms; R_3 and R_4 are each alkyl groups having from 1 to 3 carbon atoms, and X is an anion selected from halogen, acetate, phosphate, nitrate and alkyl sulfate radicals. The aliphatic groups may contain ether linkages, and other groups such as amido groups, in addition to carbon and hydrogen atoms.

Other useful quaternary ammonium salts have the formula:



wherein at least one, but no more than 3, of the R groups is an aliphatic group having from 16 to 22 carbon atoms, and the remaining R groups are selected from hydrogen and alkyl groups having from 1 to 4 carbon atoms, and X is an ion selected from halogen, acetate, phosphate, nitrate and alkyl sulfate radicals Tallow propane diammonium dichloride is an example of this type of quaternary ammonium salt.

Quaternary ammonium salts useful herein also include dialkyldimethylammonium chlorides wherein the alkyl groups have from 12 to 22 carbon atoms. These alkyl groups may be derived from long-chain fatty acids, such as hydrogenated tallow fatty acid. Tallow fatty acid gives rise to quaternary compounds wherein R_1 and R_2 predominantly have from 16 to 18 carbon atoms. Examples include ditallow dimethyl ammonium chloride, ditallow dimethyl ammonium methyl sulfate, dihexadecyl dimethyl ammonium chloride, di(hydrogenated tallow) dimethyl ammonium chloride, dioctadecyl dimethyl ammonium chloride, dieicosyl dimethyl ammonium chloride, didocosyl dimethyl ammonium chloride, di(hydrogenated tallow) dimethyl ammonium acetate, dihexadecyl dimethyl ammonium chloride, dihexadecyl dimethyl ammonium acetate, ditallow dipropyl ammonium phosphate, ditallow dimethyl ammonium nitrate, di(coconutalkyl) dimethyl ammonium chloride, and stearyl dimethyl benzyl ammonium chloride. Preferred quaternary ammonium salts useful herein include ditallow dimethyl ammonium chloride, dicetyl dimethyl ammonium chloride, stearyl dimethyl benzyl ammonium chloride, cetyl trimethyl ammonium chloride, tricetyl methyl ammonium chloride, and mixtures thereof. Di(hydrogenated tallow) dimethyl ammonium chloride (Quaternium-18) is a particularly preferred quaternary ammonium salt, and is available from the Sherex Chemical Company, Inc. as Adogen 442 and Adogen 442-100P.

Salts of primary, secondary and tertiary fatty amines may also be used as a cationic surfactant. The alkyl groups of such amines preferably have from 12 to 22 carbon atoms, and may be substituted or unsubstituted. Secondary and tertiary amines are preferred; and tertiary amines are particularly preferred. Examples of useful amines include stearamido propyl dimethyl amine, diethyl amino ethyl stearamine, dimethyl stearamine, dimethyl soyamine, soyamine, myristyl amine, tridecyl amine, ethyl stearylamine, N-tallowpropane diamine, ethoxylated (5 moles E.O.) stearylamine, dihydroxy ethyl stearylamine, and arachidylbehenylamine. Suitable amine salts include the halogen, acetate, phosphate, nitrate, citrate, lactate and alkyl sulfate salts. Examples include stearylamine hydrochloride, soyamine chloride, stearylamine formate, N-tallowpropane diamine dichloride and stearamidopropyl dimethylamine citrate. Useful cationic amine surfactants are also disclosed in U.S. Pat. No. 4,275,055 (Nachtigal et al., issued Jun. 23, 1982).

3. Water. Water is an essential ingredient in the conditioner formulations. Water is added as the last step in preparing the conditioner, using an amount sufficient to bring (q.s.) the mixture to 100%.

4. Optional Ingredients. Silicone conditioning agents may be used for their cosmetic and rheological charcteristics. Silicone oils and silicone polymers are well known conditioning agents. For example, volatile silicones, organosilicone polymers in water-alcohol mixtures, and volatile silicone fluids are disclosed in U.S. Pat. No. 5,292,502, supra.

The formulation may include one or more silicones disclosed for use in the shampoo formulations supra. Thse silicones include volatile and non-volatile polyalkyl siloxanes, polyalkylaryl siloxanes, and mixtures thereof. They may be used at levels from about 0.2% to about 5% of the final formulation.

As with shampoos, the higher viscosity silicone gums of the siloxanes disclosed supra are preferred. These gums are rigid, as opposed to a fluid, with high molecular weights of from about 200,000 to about 1,000,000 and viscosities from about 100,000 cp to about 150,000,000 cp at 25°. Most preferred are the polydimethylsiloxane gums.

Often a significant amount of the lipid material in the conditioner is deposited on the hair, leaving it greasy. The conditioner formulations may, therefore, incorporate silicone copolyols to provide optimum conditioning benefits with the anti-lice treatment. See European Patent Application 155,806, published Sep. 25, 1985.

The silicone copolyols are polyalkylene oxide modified dimethylpolysiloxanes, herein referred to as a "dimethicone copolyols" that act as an emulsifier and reduce the deposition of the vehicle materials (lipid materials and/or cationic surfactants) on the hair. Useful dimethicone copolyols are also disclosed in U.S. Pat. No. 5,292,504, supra.

The silicone copolyol is generally present at a level of from about 0.1% to about 10%, preferably from about 0.1% to about 2%, of the final formulation.

Dimethicone copolyols are preferred for this use. Dow Corning 190 Silicone Surfactant is a preferred dimethicone copolyol.

The formulations may also contain components that modify the physical and performance characteristics of the conditioning product. Such components include additional surfactants, salts, buffers, thickeners, solvents, opacifiers, pearlescent aids, preservatives, fragrance, colorants, dyes, pigments, chelators, sunscreens, vitamins, and medicinal agents. Examples of these types of components are disclosed in U.S. Pat. No. 4,387,090 (Bolich, Jr., issued Jun. 7, 1983).

The formulations may also contain optional surfactant materials at levels such that the total level of surfactant present in the formulation (including the cationic surfactant vehicle material, described supra) is from about 0.05% to about 5%. These optional surfactant materials may be anionic, nonionic or amphoteric. Examples are ceteareth-20, steareth-20, sorbitan monoesters, sodium tallow alkylsulfate, and tallow betaine. Optional surfactant materials are described in McCutcheon's Detergents & Emulsifiers, supra; Schwarts et al., supra; and U.S. Pat. No. 3,929,678 supra.

Preferred optional surfactant materials are nonionic. Such surfactants are most commonly produced by the condensation of an alkylene oxide (hydrophilic in nature) with an organic hydrophobic compound that is usually aliphatic or alkyl aromatic in nature. The length of the hydrophilic or polyalkylene moiety that is condensed with any particular hydrophobic compound can be adjusted to yield a water-soluble compound having the desired degree of balance between hydrophilic and hydrophobic elements. Such nonionic surfactants include polyethylene oxide condensates of alkyl phenols, condensation products of aliphatic alcohols with ethylene oxide, condensation products of ethylene oxide with a hydrophobic base formed by condensation of propylene oxide with propylene glycol, and condensation products of ethylene oxide with the product resulting from the reaction of propylene oxide and ethylene diamine. Another variety of nonionic surfactant is a non-polar nonionic surfactant, typified by the amine oxide surfactants. Preferred nonionic surfactants include ceteareth-20, steareth-20 and ceteth-2.

Salts and buffers may also be added in order to modify the product rheology. For example, salts such as potassium chloride, ammonium chloride, and sodium chloride, may be added at levels of form about 0.001% to about 1%. Buffers, such as citrate or phosphate buffers, may also be added. The present formulations as finally formulated preferably have a pH of from about 3 to about 10, most preferably from about 3 to about 7.

Additional conditioning components may also be incorporated into the formulations. For example, proteins may be added at levels of from about 0.1% to about 10%. Cationic proteins may also serve as surfactant vehicle materials.

Thickening agents are preferred optional components. Such thickeners include nonionic thickening agents that are incorporated at levels of from about 0.1% to about 8%. Such agents are polymers that exhibit viscosities exceeding about 20,000 cp at low shear (about 10^{-2} sec^{-1}). Examples are polyoxyethylene, guar gum, methylcellulose, methyl hydroxypropyl cellulose, polypropyl cellulose, polypropyl hydroxyethyl cellulose, hydroxyethyl cellulose, starches and starch derivatives, and mixtures thereof. Nonionic thickening agents are disclosed in U.S. Pat. No. 4,387,090 (Bolich et al., issued Jun. 7, 1983).

The thickening agents are used to bring the viscosity of the formulation from about 10,625 cp to about 14,375 cp (as measured with a Wells-Brookfield viscometer, Model RVT DV-CP-2, DV-11, Model Cone CP-52, using ½ mL at 1 rpm at 26.7°. for 1 minute).

The hair conditioning formulations of this invention are generally used on the hair after all shampoo has been removed by rinsing with water.

This invention also provides a method for treating human hair to kill and facilitate removal of lice and their eggs, comprising the steps of:

(a) applying from about 10 grams to about 30 grams of a formulation of this invention to the wet hair;

(b) working the formulation through the hair and scalp;

(c) leaving the formulation on the hair and scalp for about 6–10 minutes; and

(d) removing the formulation from the hair by rinsing with water.

III. Lotions

Anti-lice lotions comprising a spinosyn, or a physiologically acceptable derivative or salt thereof, and a lotion carrier are another aspect of this invention. These lotions can be applied directly onto the hair in liquid form or in spray form. They are formulated to be applied to the hair for a period of time and not immediately removed by rinsing with water.

A. Spinosyn Component

When used in a lotion formulation of this invention, the spinosyn component is generally present at a level of from about 0.1% to about 30%, preferably from about 1% to about 10%.

B. Liquid Vehicle

In addition to the spinosyn component, the lotion formulations of this invention comprise a liquid vehicle such as alcohol, water or a mixture thereof, to assist in delivery of the spinosyn component to the hair. Suitable alcohols are monohydric alcohols such as methanol, ethanol, isopropanol, or mixtures thereof. Since alcohols can have a deleterious effect upon the stability of the formulations, water alone is most preferred as the vehicle. The vehicle is added in an amount necessary to q.s. the formulation to 100%.

C. Optional Components

The lotion formulations of this invention may include optional components to provide benefits to the hair in addition to the anti-lice activity. Optional components include: preservatives and antimicrobials, such as DMDM hydantoin and tetrasodium EDTA; pH balancing agents, such as sodium citrate and citric acid; emulsifiers, such as PEG-60 castor oil; and thickeners and viscosity modifiers, such as polyvinylpyrrolidone. When included, such components generally are used individually at a level from about 0.01% to about 10%.

Conditioning agents may be included to facilitate the removal of dead lice and eggs from the hair and to provide good wet and dry combing. The same types of conditioning agents described in the conditioning formulations supra may be used in the lotions; these include quaternary ammonium salts, fatty amines and mixtures thereof. Conditioning agents are used at levels from about 0.1% to about 1%, preferably from about 0.4% to about 0.6%.

Preferred conditioning agents are quaternary ammonium salts. Preferred quaternary ammonium salts include dialkyldimethylammonium chlorides, wherein the alkyl groups have from 12 to 22 carbon atoms. These alkyl groups may be derived from long-chain fatty acids, such as hydrogenated tallow fatty acid. Tallow fatty acid gives rise to quaternary compounds wherein R_1 and R_2 predominantly have from 16 to 18 carbon atoms. Examples of quaternary ammonium salts useful in the lotion formulations include di(hydrogenated) tallow dimethyl ammonium chloride, dicetyl dimethyl ammonium chloride, tricetyl methyl ammonium chloride, cetyl trimethyl ammonium chloride, stearyl dimethyl benzyl ammonium chloride, and mixtures thereof. Most preferred is dicetyl dimethyl ammonium chloride.

Alcohol synergizers may also be added to the lotion formulations to enhance their anti-lice activity. The alcohols used in the lotion formulations are selected from phenyl C_2–C_6 alkanols, phenyl C_2–C_6 diols, C_2–C_8 alkylene diols, and mixtures thereof. These synergizers may be included at

levels from about 0.25% to about 10%, wherein the level of phenyl alkanols, phenyl diols, and mixtures thereof, does not exceed 5% of the formulation. Preferably, the level is about 0.5% to about 5% of the formulation, most preferably from about 2% to about 4%. A preferred synergizer is hexylene glycol.

The lotion formulations of this invention are applied directly to the hair. The amount of lotion used is generally from about 10 mL to about 50 mL. The lotion is worked through the hair and left on the hair for about 10 minutes, preferably about 30 minutes. The hair is then cleansed, generally with a shampoo, before rinsing with water.

The following examples illustrate the formulations of this invention:

EXAMPLE 1

A lotion formulation is prepared as follows:

Component	Weight (%)
Polyvinylpyrrolidone	0.50
DMDM hydantoin	0.20
Tetrasodium EDTA	0.13
Citric acid	0.05
PEG-60 castor oil	0.50
Hexylene glycol	4.00
Dicetyl dimethyl ammonium chloride	0.38
Spinosyn A	0.50
Water q.s. to	100.00

Add the spinosyn to a tank containing a mixture of PEG-60 castor oil, hexylene glycol, propylene glycol and dicetyl dimethyl ammonium chloride at between 35° to 38°. In a second tank, mix polyvinyl pyrrolidone, DMDM hydantoin, tetrasodium EDTA and citric acid and bring the mixture to a temperature between 35° to 38°. Add the contents of the first tank to the second tank and mix until uniform. Cool the mixture to about 27°, and empty into storage drums.

EXAMPLE 2

A lotion formulation is prepared using the procedure described in Example 1, but with the following formula.

Component	Weight (%)
Polyvinylpyrrolidone	0.50
DMDM hydantoin	0.20
Tetrasodium EDTA	0.13
Citric acid	0.05
PEG-60 castor oil	0.50
Hexylene glycol	2.00
Propylene glycol	2.00
Dicetyl dimethyl ammonium chloride	0.38
Spinosad	0.25
Water q.s. to	100.00

EXAMPLE 3

A lotion formulation is prepared by the procedure described in Example 1, but with the following formula:

Component	Weight (%)
Polyvinylpyrrolidone	0.50
DMDM hydantoin	0.20
Tetrasodium EDTA	0.13
Citric acid	0.05
Isopropanol	1.00
PEG-60 castor oil	0.50
Hexylene glycol	4.00
Dicetyl dimethyl ammonium chloride	0.60
Spinosyn component	0.10
Water q.s. to	100.00

To control a lice infestation, the lotion formulations of Examples 1–3 are applied to the hair and left on for at least ½ hour before being removed by shampooing or rinsing.

EXAMPLE 4

A shampoo formulation is prepared as follows:

Component	Weight (%)
Ammonium laureth sulfate	10.40
Ammonium lauryl sulfate	9.50
Coconut monoethanolamide	4.00
Ethylene glycol distearate	3.00
DMDM hydantoin	0.20
Monosodium phosphate	0.10
Disodium phosphate	0.25
Citric acid	0.07
Ammonium xylenesulfonate	1.58
Spinosyn A	0.50
Water q.s. to	100.00

Add the ammonium lauryl sulfate to a tank and heat to between about 66° to about 69°. While maintaining this temperature, add an aqueous solution of mono-sodium phosphate and then an aqueous solution of disodium phosphate. Upon reaching 69°, add the ammonium xylenesulfonate to the mixture and heat to from about 74° to 77°; add the cononut monoethanolamide, mixing until well dispersed, the ethylene glycol distearate and about 4.5% of the water. Continue mixing until homogeneous and cool mixture to about 41°. Pump the mixture into a second tank and add the ammonium laureth sulfate, DMDM hydantoin, and aqueous solution of citric acid. Add the a spinosyn to the second tank and q.s. to 100% with water. Mix thoroughly, cool to about 27°, and pump the mixture into storage drums.

EXAMPLE 5

A shampoo formulation is prepared as follows:

Component	Weight
Ammonium laureth sulfate	14.15
Ammonium lauryl sulfate	3.14
Coconut monoethanolamide	3.00
Ethylene glycol distearate	3.00
Silicone gum[1]	0.50
Dimethicone fluid (350 cp)	0.50
Tricetyl methyl ammonium chloride	0.29
Cetyl alcohol	0.42
Stearyl alcohol	0.18

-continued

Component	Weight
DMDM hydantoin	0.20
Sodium chloride	0.90
Ammonium chloride	0.05
Ammonium xylenesulfonate	1.25
Spinosad	0.40
Water q.s. to	100.00

[1]Silicone gum available from The General Electric Co. as SE-30 or SE-76 Gum.

Add approximately 0.5% of the ammonium laureth sulfate and the dimethicone to a container, and mix for approximately 30 minutes. Add approximately 2% ammonium laureth sulfate to a processing tank and heat to 68° to 71°. Add about 0.12% stearyl alcohol, about 0.06% of cetyl alcohol, and the contents of the first container to the processing tank. Mix until uniform, maintaining the mixture between 68° and 71°. To a second processing tank, add ammonium lauryl sulfate and heat to about 71°. While maintaining this temperature, add 0.05% ammonium chloride, about 18% water, ammonium xylenesulfonate and the remainder of the stearyl and cetyl alcohols. Add coconut monoethanolamide, tricetyl methyl ammonium chloride, ethylene glycol distearate, approximately half the DMDM hydantoin and the contents of the first tank to the second tank while maintaining a temperature of about 77°. Mix until homogenous and then cool to about 41°. Pump to a third tank and add the remainder of the ammonium laureth sulfate, DMDM hydantoin, and sodium chloride. Add the spinosyn to the mixture and q.s. to 100% with water. Mix thoroughly, cool to about 27°, and pump the mixture into storage drums.

EXAMPLE 6

A shampoo formulation is prepared as follows:

Component	Weight %
Ammonium laureth sulfate	12.81
Ammonium lauryl sulfate	9.10
Coconut monoethanolamide	2.30
Isostearyl ethylmidonium ethosulfate	1.25
DMDM hydantoin	0.20
Monosodium pohsophate	0.50
Disodium phosphate	0.38
Sodium chloride	0.04
Citric acid	0.10
Ammonium xylenesulfonate	1.35
Spinosyn component	0.56
Water q.s. to	100.00

Add about 6.5% of the water and the ammonium laureth sulfate to a mixing tank and heat the mixture to about 35°. While maintaining this temperature, add the following components individually in sequence, mixing so that each component is well mixed into the batch: ammonium lauryl sulfate, ammonium xylenesulfonate, monosodium phosphate, disodium phosphate, DMDM hydantoin, sodium chloride, a solution of citric acid and water, a solution of coconut diethanolamide and isostearyl ethylmidonium ethosulfate. Add the spinosyn to the mixture, and q.s. to 100% with water. Mix thoroughly, cool to about 27°, and pump the mixture into storage drums.

EXAMPLE 7

A conditioner formulation of this invention is prepared as follows:

Component	Weight %
Cetyl alcohol	1.00
Stearyl alcohol	0.72
DMDM hydantoin	0.20
Hydroxyethyl cellulose	0.50
Quaternium-18	0.85
Ceteareth-20	0.35
Stearalkonium chloride	0.85
Glyceryl monostearate	0.25
Citric acid	0.08
Silicone gum[1]	0.30
Cyclomethicone fluid	1.70
Spinosyn A	1.00
Water q.s. to	100.00

[1]Silicone gum available from The General Electric Co. as SE-30 or SE-76 Gum.

Combine all components, except the DMDM hydantoin, citric acid, silicone gum, cyclomethicone, and a spinosyn, in a processing tank and heat the mixture to about 88°. After the solution is thoroughly mixed, cool it to approximately 48°. In a separate tank, premix the silicone gum and cyclomethicone, with heat and agitation to form a gum solution. Add the spinosyn to this mixture. Add the gum solution and all the remaining components, and q.s. with water. Mix thoroughly, cool to about 27°, and pump the mixture into storage drums.

EXAMPLE 8

A conditioner formulation is prepared by the procedure described in Example 7, but using the following formula:

Component	Weight %
Cetyl alcohol	1.00
Stearyl alcohol	0.72
DMDM hydantoin	0.20
Hydroxyethyl cellulose	0.50
Quaternium-18	0.85
Ceteareth-20	0.35
Stearamidopropyldimethyl amine (SAPDMA)	0.50
Glyceryl monostearate	0.25
Citric acid	0.08
Sodium Citrate	0.05
Stearoxydimethicone	0.10
Silicone gum[1]	0.05
Cyclomethicone fluid	1.70
Spinosyn component	1.00
Water q.s. to	100.00

[1]Silicone gum available from The General Electric Co. as SE-30 or SE-76 Gum.

This conditioner anti-lice product is made in a manner similar to that described in Example 7.

EXAMPLE 9

Efficacy of Shampoo Formulations

Shampoo formulations containing various concentrations of spinosad were used in this study. The formulations were prepared by wet milling for 30 minutes enough technical grade spinosad into a commercially available shampoo (Johnson's® Baby Shampoo, Moisturizing Formula with Honey and Vitamin E, Johnson & Johnson Consumer Products, Inc.) to form a 10% stock spinosad/shampoo mixture. This mixture was diluted with additional shampoo to prepare the following spinosad concentrations: 10% (used

as originally prepared), 1%, 0.1% and 0.01% spinosad/shampoo (w/w).

The four concentrations of spinosad in shampoo and a control of tap water were tested against adult human body lice (*Pediculus humanus humanus*) according to a standard test, ASTM Standard E 938-83 (Reapproved 1988), that is available from the American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, Penn. USA [http://www.astm.org/]. In this test, 25 adult lice were immersed in each of the four shampoo concentrations for 10 minutes, then washed in water for 1 minute and rinsed in water for another minute. In the control group, 25 adult lice (*Pediculus humanus humanus*) were immersed in tap water for 10 minutes, then washed in water for 1 minute, and rinsed in water for another minute. A total of 5 trials were performed.

After one hour, the lice were examined to determine the knockdown number. "Knockdown" was measured as the rather quick (within a matter of one minute) immobilization of insect activity which leads from a moribund state to a state of kill. After 24 hours, the lice were again examined to determine the number killed. The results of this study are summarized in Table 1.

TABLE 1

Comparison of Pediculicidal Effects of Spinosad in Shampoo at Various Concentrations Mortality Data

Formulation	+1 hour % Knockdown	+24 hours % Mortality
Control	0.2	1.0
10% spinosad/shampoo	96.6	100.0
1% spinosad/shampoo	48.0	100.0
0.1% spinosad/shampoo	19.8	97.4
0.01% spinosad/shampoo	14.7	35.5

The study showed that shampoo formulations containing 1% and 10% spinosad were highly effective pediculicides, providing a +24 hour mortality of 100%. The 10% concentration gave the quickest knockdown effect (96.6% at +1 hour), and even the 1% concentration provided a knockdown rate of 48%. The 0.1% spinosad/shampoo formulation was also an effective pediculicide, providing nearly 100% mortality after 24 hours.

I claim:

1. A pediculicidal hair conditioner formulation comprising as an active ingredient from about 0.1% to about 30% of a spinosyn, or a physiologically acceptable derivative or salt thereof, a conditioner and water.

2. The conditioner formulation of claim 1 wherein the active ingredient is from about 1% to about 10% of the spinosyn.

3. The conditioner formulation of claim 1 wherein the conditioner is a long chain quaternary ammonium compound combined with a lipid material.

4. The conditioner formulation of claim 3 wherein the lipid material is present at a level of from about 0.5% to about 3% of the formulation..

5. The conditioner formulation of claim 1 which further comprises a surfactant.

6. The conditioner formulation of claim 5 wherein the surfactant is present at a level of from 0.1% to about 5% of the formulation.

7. An anti-lice lotion comprising a spinosyn, or a physiologically acceptable derivative or salt thereof, a conditioner and a liquid vehicle.

8. The lotion of claim 7 wherein the spinosyn is present at a level of from about 0.1% to about 30% of the lotion.

9. The lotion of claim 8 wherein the spinosyn is present at a level of from about 1% to about 10% of the lotion.

10. The lotion of claim 7 wherein the liquid vehicle is water.

11. The lotion of claim 7 wherein the liquid vehicle is a monohydric alcohol.

12. The lotion of claim 7 wherein the conditioning agent is a quaternary ammonium salt.

* * * * *

EXHIBIT D

CERTIFICATION OF FACSIMILE TRANSMISSION

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Susan Buis
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Susan Buis 8-24-01
Signature Date

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Daniel Earl Snyder	)
Serial No.	:	09/543,441	)
Filed	:	April 5, 2000	) Group Art Unit: 1614
For	:	FORMULATIONS FOR CONTROLLING HUMAN LICE	) Examiner: R. Cook
Docket No.	:	X-12227A	)

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Assistant Commissioner for Patents
Washington, D. C. 20231
Sir:

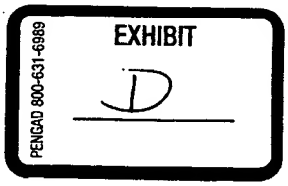
Identification of Person Making This Disclaimer

I, John C. Demeter, am employed by Eli Lilly and Company, and I am an attorney of record in the above-identified patent application. In that capacity, I am authorized to sign this disclaimer on behalf of Eli Lilly and Company.

Identity of Assignee

I hereby verify that the assignee owning all of the interest in this application is:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285



Recordal of Assignment in PTO

The assignment was recorded on June 22, 1999, Reel 10056, Frame 0605.

Extent of Interest

The extent of Eli Lilly and Company's interest is in the whole of this invention.

Disclaimer

I hereby disclaim the terminal part of any patent granted on this application, which would extend beyond the expiration date of:

United States Patent No. 6,063,771 and hereby agree that any patent granted on this application shall be enforceable only for and during such period that the legal title to the patent shall be the same as the legal title to United States Patent No. 6,063,771.

I do not disclaim any terminal part of any patent granted on this application prior to the expiration date of the full statutory term of United States Patent No. 6,063,771 in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims cancelled by a reexamination certificate, or is otherwise terminated prior to expiration of its full statutory term other than as presently shortened by any terminal disclaimer.

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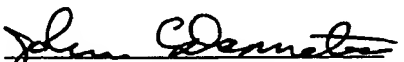
By: 

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EXHIBIT E

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Patent Bibliographic Data					03/07/2011 07:12 PM
Patent Number:	6342482		**Application Number:**	09543441	
Issue Date:	01/29/2002		**Filing Date:**	04/05/2000	
Title:	Formulations for controlling human lice				
Status:	12th year fee window opens: 01/29/2013			**Entity:**	Large
Window Opens:	01/29/2013	**Surcharge Date:**	07/30/2013	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:	1553	MAINTENANCE FEE DUE AT 11.5 YEARS			
Surcharge Fee Code:					
Most recent events (up to 7):	06/22/2009 06/30/2005	Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
Address for fee purposes:	ELI LILLY & COMPANY PATENT DIVISION P.O. BOX 6288 INDIANAPOLIS, IN 462066288				

Run Another Query

Need Help? | USPTO Home Page | Finance Online Shopping Page | Alerts Page

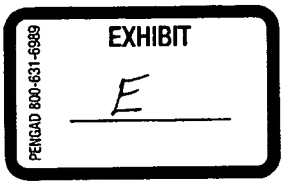


EXHIBIT F

aventor
medical technology, from start to finish

8 October 2004

Ms. Jacquelyn Smith
Regulatory Project Manager
FDA
CDER/OND/DDDDP
Building CRP2, Rm. 236
Rockville MD 20850

Re: IND 66,657

Dear Ms. Smith,

Enclosed is IND 66,657, Spinosad Crème Rinse for the Treatment of Human Head Lice. Per FDA requirements three copies are being submitted.

As the FDA is aware Spinosad has undergone extensive toxicological evaluations as part of the agrochemical registration program. In the pre-IND Meeting held between the FDA and representatives of both ParaPRO and Aventor on 12 May 2003 the FDA requested that the initial IND contain detailed study reports for all nonclinical studies. Therefore, this IND contains, as background material, 19 volumes which are copies of the of toxicology studies of Spinosad. In the May 2003 meeting the FDA requested that the initial IND not include the detailed carcinogenicity study reports. Accordingly this IND contains a summary of the carcinogenicity study reports.

The primary IND, which consists of two volumes, contains several attachments that are not very clear. Please understand that these are the best copies that are available.

Please contact me if you have any questions.

Sincerely,

O. Reed Tarwater, Ph.D., RAC
Senior Regulatory Consultant
Aventor, LLC

PENGAD 800-631-6989 EXHIBIT F

EXHIBIT G

PRO ANSON GROUP

Susan Walker. MD
Division Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
59010-B Ammendale Road
Beltsville, MD 20705-1266

21 January 2009

Re: NDA 22-408, NatrOVA™ for the Treatment of Human Head Lice and Nits

Enclosed is the New Drug Application (22-408) submitted by ParaPRO LLC for NatrOVA for the Treatment of Human Head Lice and Nits.

The information is presented via the electronic CTD format, which has been reviewed by the FDA prior to this submission. Further, NDA 22-408 was submitted electronically as an e-CTD by QST Consultations, Ltd.

Information requested from the pre-NDA meeting on 4 November 2008 can be found in section 5.4.

Please contact me if you have questions. We look forward to working with the Agency on this application.

Sincerely yours,

O. Reed Tarwater, Ph.D., RAC
Director, Anson Group and Regulatory Consultant to ParaPRO

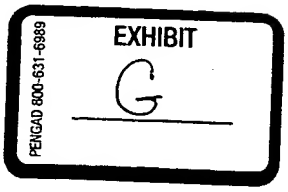


EXHIBIT H

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-408

NDA ACKNOWLEDGMENT

ParaPro Pharmaceuticals, LLC
c/o Anson Group
Attention: O. Reed Tarwater, Ph.D., RAC
Director
11460 N. Meridian Street, Suite 150
Carmel, IN 46032

Dear Dr. Tarwater:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Spinosad Cream Rinse, 1%

Date of Application: January 21, 2009

Date of Receipt: January 22, 2009

Our Reference Number: NDA 22-408

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 20, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been

met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,* to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me, at (301) 796-2311.

Sincerely,

[Not approved for use as signature per FDA]
Catherine Carr, MSc.
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Catherine Carr
3/4/2009 12:12:21 PM

EXHIBIT I

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022408

NDA APPROVAL

ParaPRO, LLC
Attention: William Culpepper, III
President
11550 N. Meridian St., Suite 600
Carmel, IN 46032

Dear Mr. Culpepper:

Please refer to your New Drug Application (NDA) dated January 21, 2009, received January 22, 2009, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Natroba (spinosad) Topical Suspension, 0.9%.

We acknowledge receipt of your amendments dated February 25, March 10 and 31, May 1, June 29, July 9 and 16, August 21, September 8 and 24, December 11 and 30, 2009; January 26, April 16, May 25, June 14, July 23, September 14 and 23, November 23, December 16, 2010, and January 11, 2011.

The July 23, 2010, submission constituted a complete response to our November 18, 2009 action letter.

This new drug application provides for the use of Natroba (spinosad) Topical Suspension, 0.9% for the topical treatment of head lice infestation in patients 4 years of age and older.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your December 16, 2010, submission containing final printed carton and container labels.

Your application for Natroba (spinosad) Topical Suspension, 0.9% was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues in the intended population.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 months to 6 months because this product would be unsafe in this pediatric subpopulation, since it contains benzyl alcohol and there is a risk of benzyl alcohol toxicity. This product is not recommended for use in neonates and infants below the age of 6 months. In addition, necessary studies are impossible or highly impracticable because there are too few children with the condition to study. This product also does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this pediatric subpopulation and is not likely to be used in a substantial number of pediatric patients in this subpopulation

We are deferring submission of your pediatric studies for ages 6 months to 4 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed in those patients with head lice infestation.

Your deferred pediatric study required by 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act.

Your deferred pediatric study under PREA is as follows:

1711 A pharmacokinetic and safety study in pediatric patients ages 6 months to 4 years of age with active head lice infestation. This study should be conducted under maximum use conditions and include a minimum of 24 evaluable patients who will undergo pharmacokinetic sampling and assessments of local and systemic safety at appropriate time points.

The timetable you submitted on September 14, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission: March, 2011

Study Completion: December, 2011

Final Study Report Submission: March, 2012

Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment**".

Submit clinical protocols to your IND 066657 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing studies should be prominently labeled "**Postmarketing Requirement Protocol,**" "**Postmarketing Requirement Final Report,**" or "**Postmarketing Requirement Correspondence.**"

This product is appropriately labeled for use in ages 4 to 16 years for this indication. Therefore, no additional studies are needed in this pediatric age group.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues

Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application. If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

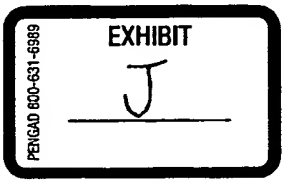
/s/

JULIE G BEITZ
01/18/2011
Change the set number to 1711-1

Reference ID: 2892678

EXHIBIT J

Correspondence Date	Correspondence between PARAPro and FDA regarding Natroba	Type of Correspondence
2004		
September 24, 2004	Correspondence from PARAPro to FDA regarding pre-Investigational New Drug (IND) Briefing Document	Letter
September 29, 2004	Initial submission of IND application from PARAPro to FDA	Submission
September 30, 2004	Correspondence from PARAPro to FDA requesting meeting to discuss preclinical program	Letter
October 5, 2004	Correspondence from PARAPro to FDA regarding change in initial protocol	Submission
October 6, 2004	Correspondence from FDA to PARAPro regarding submission of IND for official review	Fax
October 8, 2004	Revised submission of IND application from PARAPro to FDA	Submission
October 12, 2004	Correspondence from FDA to PARAPro acknowledging receipt and acceptance of IND application submitted on October 8, 2004	Email
November 3, 2004	Correspondence between PARAPro and FDA regarding clinical endpoints for Protocol No. SPN-101-04	Teleconference
November 3, 2004	Correspondence from PARAPro to FDA regarding changes to Protocol No. SPN-101-04	Fax
November 19, 2004	Correspondence from FDA to PARAPro regarding November 3, 2004 teleconference	Fax
December 16, 2004	Correspondence from FDA to PARAPro regarding clinical comments for IND	Fax
2005		
January 4, 2005	Correspondence from PARAPro to FDA responding to clinical comments from FDA received on December 16, 2004	Letter
January 31, 2005	Correspondence from PARAPro to FDA requesting meeting regarding juvenile neurotoxicology study	Letter
February 2, 2005	Correspondence from PARAPro to FDA regarding change in initial protocol	Submission
February 3, 2005	Correspondence from FDA to PARAPro regarding request for Type A Meeting	Email
February 9, 2005	Correspondence from FDA to PARAPro reporting that meeting request for juvenile neurotoxicology study is premature	Letter



February 16, 2005	Correspondence from PARAPro to FDA regarding pediatric pharmacokinetic study	Submission
March 10, 2005	Correspondence from PARAPro to FDA regarding single dose human pharmacokinetic study	Submission
May 3, 2005	Correspondence from PARAPro to FDA regarding single dose study in pediatric patients and report on Protocol No. SPN-101-04	Submission
May 12, 2005	Correspondence from FDA to PARAPro regarding correspondence of September 24, 2004 and advising submission of IND application	Fax
May 18, 2005	Correspondence from PARAPro to FDA resubmitting neurotoxicity documents originally sent on September 24, 2004	Submission
May 23, 2005	Correspondence from PARAPro to FDA requesting Type A Meeting	Submission
June 21, 2005	Correspondence from FDA to PARAPro regarding request for Type A Meeting and IND materials	Fax
June 21, 2005	Correspondence from FDA to PARAPro regarding comments of FDA pharmacology and toxicology reviewer	Fax
June 21, 2005	Correspondence from PARAPro to FDA inquiring about comments by FDA pharmacology and toxicology reviewer	Teleconference
June 27, 2005	Correspondence from FDA to PARAPro regarding responses by FDA pharmacology and toxicology reviewer	Fax
September 20, 2005	Correspondence from PARAPro to FDA regarding Protocol No. SPN-201-05	Submission
October 20, 2005	Correspondence from PARAPro to FDA regarding final Serious Adverse Event (SAE) reports for combined skin irritation sensitization study	Submission
October 21, 2005	Correspondence from FDA to PARAPro regarding report of 2 SAE report forms for Protocol No. SPN-201-05	Letter
December 5, 2005	Annual Report submission from PARAPro to FDA regarding combined skin irritation sensitization study	Submission
December 16, 2005	Correspondence from PARAPro to FDA regarding new protocol request for review	Submission

2006		
January 4, 2006	Correspondence from PARAPro to FDA submitting IND Annual Report and protocol outline for Phase 2 study	Letter
January 17, 2006	Correspondence between PARAPro and FDA regarding Phase 2S study protocol	Teleconference
January 31, 2006	Correspondence from PARAPro to FDA regarding seven volumes of study report for skin irritation and sensitization study	Submission
February 6, 2006	Correspondence from PARAPro to FDA regarding SPN-103-05	Submission
February 7, 2006	Correspondence between PARAPro and FDA regarding approval of Phase 2B protocol	Teleconference
February 8, 2006	Correspondence from PARAPro to FDA regarding SPN-201-05	Submission
February 14, 2006	Correspondence from PARAPro to FDA regarding 18-month mouse and 2-year rat study	Submission
March 1, 2006	Correspondence from PARAPro to FDA regarding SPN-202-06	Submission
March 6, 2006	Correspondence from PARAPro to FDA regarding submission of report for Protocol No. SPN-103-05 to replace lost submission previously sent on February 6, 2006	Letter
April 10, 2006	Correspondence from PARAPro to FDA regarding Protocol No. SPN-202-06	Submission
April 13, 2006	Correspondence from PARAPro to FDA regarding Protocol No. SPN-202-06	Submission
May 18, 2006	Correspondence from PARAPro to FDA regarding Protocol No. SPN-202-06	Submission
July 26, 2006	Correspondence from PARAPro to FDA requesting end of Phase 2 meeting pursuant to 21 C.F.R. § 312.47(B)(1)	Submission
July 27, 2006	Correspondence from PARAPro to FDA submitting CMC information	Submission
August 8, 2006	Correspondence from PARAPro to FDA submitting briefing package and requesting End of Phase 2 Meeting pursuant to 21 C.F.R. § 312.47(B)(1)	Submission
August 14, 2006	Correspondence from FDA to PARAPro regarding scheduling of Type B meeting	Fax
September 14, 2006	Correspondence from PARAPro to FDA submitting final study report for Protocol No. SPN-202-06	Submission

September 21, 2006	Correspondence from PARAPro to FDA submitting CMC information	Submission
September 25, 2006	Correspondence from PARAPro to FDA submitting End of Phase 2 Meeting briefing document	Submission
October 31, 2006	End of Phase 2 Meeting between PARAPro and FDA	Meeting
November 21, 2006	Correspondence from FDA to PARAPro regarding minutes of End of Phase 2 Meeting	Fax
November 28, 2006	Correspondence from PARAPro to FDA submitting IND Annual Report	Submission
December 6, 2006	Correspondence from PARAPro to FDA acknowledging receipt of minutes of End of Phase 2 Meeting and indicating differences of understanding between PARAPro and FDA	Submission
December 8, 2006	Correspondence from PARAPro to FDA submitting long-term toxicity studies	Submission
December 11, 2006	Correspondence between PARAPro and FDA regarding differences of understanding set forth in previous submission of December 6, 2006	Teleconference
December 11, 2006	Correspondence from PARAPro to FDA regarding Protocol No. SPN-106-07 (*sic*, SPN-106-06)	Submission
December 14, 2006	Correspondence from PARAPro to FDA correcting protocol number indicated in submission of December 11, 2006 (i.e., Protocol No. SPN-106-07) to Protocol No. SPN-106-06	Submission
2007		
January 30, 2007	Correspondence from PARAPro to FDA requesting Type A Meeting with the Division of Dermatology and Dental Products to resolve CMC critical path issue for IND	Submission
February 9, 2007	Correspondence between PARAPro and FDA regarding Phase 2 and applicability of the combination drug rule (pursuant to 21 C.F.R. § 300.500)	Teleconference
March 6, 2007	Correspondence from FDA to PARAPro regarding meeting minutes from February 9, 2007 teleconference	Fax
March 9, 2007	Correspondence from PARAPro to FDA submitting Protocol No. SPN-203-07	Submission

March 9, 2007	Correspondence from PARAPro to FDA regarding correspondence of March 6, 2007, specifically lack of timeframe for the resolution of the combination drug rule by ONDQA	Submission
March 12, 2007	Correspondence from PARAPro to FDA submitting final report for Protocol No. SPN-106-06	Submission
March 22, 2007	Correspondence from PARAPro to FDA requesting Type A Meeting with the Division of Dermatology and Dental Products to resolve CMC critical path issue for IND	Submission
April 2, 2007	Correspondence from FDA to PARAPro regarding ONDC meeting to discuss combination drug rule	Teleconference
April 11, 2007	Correspondence from FDA to PARAPro regarding scheduling of guidance meeting for May 21, 2007	Fax
April 16, 2007	Correspondence from PARAPro to FDA accepting meeting date of May 21, 2007 and acknowledging COER's agreement to being Special Protocol Assessment (SPA) review	Submission
April 23, 2007	Correspondence between PARAPro and FDA regarding applicability of the combination drug rule (pursuant to 21 C.F.R. § 300.500)	Teleconference
April 24, 2007	Correspondence from PARAPro to FDA regarding combination drug rule discussed during April 23, 2007 meeting	Submission
April 26, 2007	Correspondence from PARAPro to FDA regarding submission of study comparing efficacies of spinosad A, spinosad D, and spinosad A+D	Submission
May 2, 2007	Correspondence from FDA to PARAPro regarding official minutes of April 23, 2007 meeting	Fax
May 3, 2007	Correspondence from PARAPro to FDA submitting Briefing Document in support of May 21, 2007 meeting	Submission
May 4, 2007	Correspondence from FDA to PARAPro requesting information spinosyn composition used in studies	Fax
May 7, 2007	Correspondence from PARAPro to FDA in response to May 4, 2007 request	Submission

May 11, 2007	Correspondence from FDA to PARAPro regarding applicability of the combination drug rule	Fax
May 17, 2007	Correspondence from FDA to PARAPro regarding decision that combination drug rule does not apply to spinosad	Fax
May 18, 2007	Correspondence from PARAPro to FDA submitting request for SPA	Submission
June 25, 2007	Correspondence from PARAPro to FDA regarding review of Phase 3 Protocol and SPA	Email
June 25, 2007	Correspondence from FDA to PARAPro regarding response to correspondence of December 6, 2006	Fax
June 26, 2007	Correspondence from FDA to PARAPro indicating review of SPA	Fax
June 28, 2007	Correspondence from PARAPro to FDA submitting documents for discussion during meeting on June 29, 2007	Email
June 29, 2007	Correspondence between PARAPro and FDA regarding operational questions and additional comments	Teleconference
July 31, 2007	Correspondence from FDA to PARAPro regarding completion of review of Phase 3 Protocol and SPA	Fax
August 1, 2007	Correspondence from FDA to PARAPro regarding comments and requested changes to SPA	Fax
September 19, 2007	Correspondence from PARAPro to FDA regarding submission of Phase 3 Protocol No. SPN-301-07	Submission
September 19, 2007	Correspondence from PARAPro to FDA regarding submission of Phase 3 Protocol No. SPN-302-07	Submission
September 28, 2007	Correspondence from PARAPro to FDA regarding submission of amendment to Protocol No. SPN-301-07 and investigator documents	Submission
October 1, 2007	Correspondence from PARAPro to FDA regarding submission of amendment to Protocol No. SPN-302-07 and investigator documents	Submission

November 15, 2007	Correspondence from PARAPro to FDA regarding submission of amendment to Protocol No. SPN-301-07 and investigator documents	Submission
November 15, 2007	Correspondence from PARAPro to FDA regarding submission of amendment to Protocol No. SPN-302-07 and investigator documents	Submission
November 15, 2007	Correspondence from PARAPro to FDA submitting protocol and associated documents for phototoxicity studies of formulation	Submission
December 6, 2007	Correspondence from PARAPro to FDA regarding protocol violation at single site for Protocol No. SPN-301-07	Submission
December 13, 2007	Correspondence from PARAPro to FDA submitting IND Annual Report and Clinical Investigators Brochure	Submission
December 20, 2007	Correspondence from PARAPro to FDA regarding change of sponsor representative for PARAPro	Submission
2008		
January 9, 2008	Correspondence from PARAPro to FDA regarding addition of two clinical trial sites for SPN-301-07	Submission
January 10, 2008	Correspondence from PARAPro to FDA submitting Protocol No. SPN-108-08	Submission
February 11, 2008	Correspondence from FDA to PARAPro regarding comments to IND submissions SN:046, SN:047, SN:048, SN:049, SN:050, and SN:051	Fax
February 19, 2008	Correspondence from PARAPro to FDA submitting response to comments of February 11, 2008	Submission
February 27, 2008	Correspondence from PARAPro to FDA regarding minor amendments to Protocol No. SPN-301-07	Submission
February 27, 2008	Correspondence from PARAPro to FDA regarding minor amendments to Protocol No. SPN-302-07	Submission
February 28, 2008	Correspondence from PARAPro to FDA submitting Medwatch SAE Reporting Form for Protocol No. SPN-301-07	Submission
April 28, 2008	Correspondence from PARAPro to FDA submitting Medwatch SAE Reporting Form for Protocol No. SPN-302-07	Submission

June 24, 2008	Correspondence from PARAPro to FDA requesting PDUFA NDA waiver	Submission
August 7, 2008	Correspondence from PARAPro to FDA requesting pre-NDA meeting	Submission
August 8, 2008	Correspondence from PARAPro to FDA submitting final report for Protocol No. SPN-107-07	Submission
August 11, 2008	Correspondence from PARAPro to FDA submitting final report for Protocol No. SPN-108-08	Submission
August 20, 2008	Correspondence between PARAPro and FDA regarding pre-NDA meeting	Teleconference
August 20, 2008	Correspondence from PARAPro to FDA regarding updated request for pre-NDA meeting	Email
September 3, 2008	Correspondence from FDA to PARAPro regarding scheduling of pre-NDA meeting	Teleconference
September 8, 2008	Correspondence from FDA to PARAPro regarding FDA grant of request for NDA small business waiver	Letter
October 2, 2008	Correspondence from PARAPro to FDA submitting copies of pre-NDA briefing document	Submission
October 29, 2008	Correspondence from FDA to PARAPro regarding pre-NDA briefing document	Email
November 3, 2008	Correspondence from FDA to PARAPro regarding pre-NDA meeting	Fax
November 3, 2008	Correspondence from FDA to PARAPro requesting submission of a sample of the dosing form of product	Email
November 3, 2008	Correspondence from PARAPro to FDA confirming submission of samples of the dosing form of product	Email
November 4, 2008	Pre-NDA meeting between PARAPro and FDA to discuss pre-NDA briefing document	Teleconference
November 10, 2008	Correspondence from PARAPro to FDA submitting comments for pre-NDA meeting on November 4, 2008	Submission
November 12, 2008	Correspondence from PARAPro to FDA submitting IND Annual Report	Submission
November 21, 2008	Correspondence from FDA to PARAPro regarding official minutes of pre-NDA meeting on November 4, 2008	Fax
November 25, 2008	Correspondence from PARAPro to FDA requesting a correction to official minutes of pre-NDA meeting on November 4, 2008	Submission

2009		
January 19, 2009	Correspondence from PARAPro to FDA updating and replacing the entire original master file and authorizing the use of the updated file in support of an NDA	Submission
January 22, 2009	Correspondence from PARAPro to FDA submitting NDA	Submission
February 23, 2009	Correspondence from FDA to PARAPro transmitting the FDA Guidance Document for submission of a request for review of proprietary/trade name	Email
February 23, 2009	Correspondence from PARAPro to FDA regarding request for review of proprietary/trade name	Email
February 25, 2009	Correspondence from PARAPro to FDA submitting Request for Proprietary Name Review	Submission
March 4, 2009	Correspondence from FDA to PARAPro regarding NDA acknowledgement letter	Fax
March 5, 2009	Correspondence from FDA to PARAPro regarding preliminary notice of potential filing issues (e.g., information to establish the identity of the drug substance)	Fax
March 10, 2009	Correspondence from PARAPro to FDA submitting request for FDAAA compliance documentation	Submission
March 17, 2009	Correspondence between PARAPro and FDA regarding potential filing issues	Teleconference
March 17, 2009	Correspondence from FDA to PARAPro regarding discussion points from CMC reviewer during teleconference of March 17, 2009	Email
March 18, 2009	Correspondence from PARAPro to FDA submitting response to potential filing issues discussed during teleconference of March 17, 2009	Email
March 26, 2009	Correspondence from PARAPro to FDA submitting final Medwatch SAE Reporting form for Protocol No. SPN-302-07	Letter
March 30, 2009	Correspondence from PARAPro to FDA submitting roles and obligations of clinical trials transferred from PARAPro to Concentrics Research	Submission
March 30, 2009	Correspondence from PARAPro to FDA submitting final Medwatch SAE Reporting form for Protocol No. SPN-301-07	Letter

April 7, 2009	Correspondence from FDA to PARAPro regarding 74-day Filing Review Letter	Fax
May 1, 2009	Correspondence from PARAPro to FDA submitting response to 74-day Filing Review Letter	Submission
May 27, 2009	Correspondence from FDA to PARAPro regarding conditionally acceptable status of proprietary name request	Fax
June 19, 2009	Correspondence from FDA to PARAPro regarding study reports for long term carcinogenicity studies	Fax
June 26, 2009	Correspondence from FDA to PARAPro regarding Information Request Letter	Fax
June 26, 2009	Correspondence from PARAPro to FDA submitting response to 74-day Filing Review Letter to provide additional data regarding viscosity and closure	Submission
July 10, 2009	Correspondence from PARAPro to FDA submitting study reports for long term carcinogenicity studies	Submission
July 15, 2009	Correspondence from PARAPro to FDA submitting response to Information Request Letter of June 26, 2009	Submission
August 7, 2009	Correspondence from PARAPro to FDA submitting responses to Information Request Letter of June 26, 2009	Email
September 3, 2009	Correspondence from FDA to PARAPro regarding Information Request Letter	Fax
September 3, 2009	Correspondence from FDA to PARAPro regarding executive CAC review and comments	Fax
September 8, 2009	Correspondence from PARAPro to FDA submitting further response to Information Request Letter of June 26, 2009	Submission
September 9, 2009	Correspondence from PARAPro to FDA confirming submission of samples of the dosing form of product	Email
September 24, 2009	Correspondence from PARAPro to FDA submitting further response to Information Request Letter of June 26, 2009	Submission
November 18, 2009	Correspondence from FDA to PARAPro regarding Complete Response Letter and recommendations for approval	Fax
November 18, 2009	Correspondence between PARAPro and FDA regarding Complete Response Letter	Teleconference

December 10, 2009	Correspondence from PARAPro to FDA submitting IND/NDA Annual Report	Submission
December 29, 2009	Correspondence from PARAPro to FDA submitting response to Complete Response Letter of November 18, 2009	Submission
December 30, 2009	Correspondence from PARAPro to FDA requesting Type A Meeting	Submission
2010		
January 19, 2010	Correspondence from PARAPro to FDA confirming scheduling of Type A Meeting for February 9, 2010	Email
January 22, 2010	Correspondence from PARAPro to FDA submitting response to Complete Response Letter and Briefing Document	Submission
February 1, 2010	Correspondence from PARAPro to FDA regarding spinosad/benzyl alcohol solubilization	Email
February 3, 2010	Correspondence from PARAPro to FDA regarding rescheduling of February 9, 2010 Type A Meeting	Email
February 12, 2010	Correspondence from FDA to PARAPro regarding inclement weather and closure of FDA offices	Email
February 24, 2010	Correspondence from FDA to PARAPro requesting additional delay to reschedule Type A Meeting	Email
March 9, 2010	Correspondence from FDA to PARAPro scheduling Type A Meeting on March 25, 2010	Email
March 24, 2010	Correspondence from FDA to PARAPro regarding list of meeting attendees and preliminary comments for Type A Meeting	Email
March 25, 2010	Type A Meeting between FDA and PARAPro	Meeting
April 9, 2010	Correspondence from FDA to PARAPro regarding official minutes from March 25, 2010 Type A Meeting	Email
April 16, 2010	Correspondence from PARAPro to FDA submitting response to Type A Meeting minutes and information request	Submission
May 24, 2010	Correspondence between PARAPro and FDA regarding consideration of benzyl alcohol as an active ingredient in product	Teleconference
May 25, 2010	Correspondence from PARAPro to FDA submitting list of clarifications and inquiries for CMC reviewers	Email

May 25, 2010	Correspondence from PARAPro to FDA submitting request for proprietary name review	Submission
May 28, 2010	Correspondence from FDA to PARAPro responding to clarifications and inquires of May 25, 2010	Email
June 8, 2010	Correspondence from PARAPro to FDA requesting input on proprietary/trade name change submission denial	Email
June 8, 2010	Correspondence from FDA to PARAPro regarding proprietary/trade name change submission	Email
July 12, 2010	Correspondence from FDA to PARAPro confirming reversal of FDA's decision to list benzyl alcohol as an active ingredient	Teleconference
July 21, 2010	Correspondence from FDA to PARAPro indicating that NDA review will proceed with the understanding that benzyl alcohol is not an active ingredient	Teleconference
July 23, 2010	Correspondence from PARAPro to FDA submitting Complete Response indicating benzyl alcohol is not an active ingredient	Submission
August 16, 2010	Correspondence from PARAPro to FDA regarding most recently submitted product label	Email
September 10, 2010	Correspondence from FDA to PARAPro requesting submission of various CMC items and pediatric plan	Email
September 10, 2010	Correspondence from FDA to PARAPro responding to request for various CMC items	Email
September 14, 2010	Correspondence from PARAPro to FDA submitting information request response	Submission
September 20, 2010	Correspondence from PARAPro to FDA submitting timeline for pharmacokinetic study	Email
September 20, 2010	Correspondence between PARAPro and FDA regarding CMC stability	Teleconference
September 21, 2010	Correspondence from PARAPro to FDA providing requested list of field reviewer names and product specification rationale	Email
September 23, 2010	Correspondence from PARAPro to FDA submitting product specification	Submission
September 30, 2010	Correspondence from FDA to PARAPro regarding product carton packaging	Email
October 1, 2010	Correspondence between PARAPro and FDA regarding pediatric plan	Teleconference

October 1, 2010	Correspondence from PARAPro to FDA providing pediatric plan information and waiver	Email
October 8, 2010	Correspondence from FDA to PARAPro regarding product carton and container packaging	Email
October 11, 2010	Correspondence from PARAPro to FDA providing edits to product carton and container packaging	Email
October 14, 2010	Correspondence from FDA to PARAPro regarding product carton and container packaging	Email
October 14, 2010	Correspondence from PARAPro to FDA providing edits to product carton and container packaging	Email
October 25, 2010	Correspondence from FDA to PARAPro regarding product carton and container packaging	Email
October 25, 2010	Correspondence from PARAPro to FDA providing edits to product carton and container packaging	Email
October 28, 2010	Correspondence from FDA to PARAPro indicating approval of proprietary/trade name "Natroba"	Letter
October 29, 2010	Correspondence from FDA to PARAPro regarding product carton and container packaging	Email
November 1, 2010	Correspondence from PARAPro to FDA providing edits to product carton and container packaging	Email
November 4, 2010	Correspondence from FDA to PARAPro regarding product labeling information	Email
November 9, 2010	Correspondence from PARAPro to FDA providing edits to product labeling information	Email
November 23, 2010	Correspondence from PARAPro to FDA submitting IND/NDA Annual Report	Submission
December 14, 2010	Correspondence from FDA to PARAPro regarding product labeling information	Email
December 14, 2010	Correspondence from PARAPro to FDA providing edits to product labeling information	Email
December 15, 2010	Correspondence from FDA to PARAPro regarding product labeling information	Email

December 15, 2010	Correspondence from PARAPro to FDA providing edits to product labeling information	Email
December 16, 2010	Correspondence from FDA to PARAPro regarding product labeling information	Email
December 16, 2010	Correspondence from PARAPro to FDA submitting edits to product labeling information	Submission
December 22, 2010	Correspondence from FDA to PARAPro regarding product labeling information	Email
2011		
January 7, 2011	Correspondence from FDA to PARAPro regarding product labeling information	Email
January 11, 2011	Correspondence from FDA to PARAPro regarding product labeling information	Email
January 11, 2011	Correspondence from PARAPro to FDA submitting edits to product labeling information	Submission
January 18, 2011	Approval letter for Natroba issued by FDA	Email